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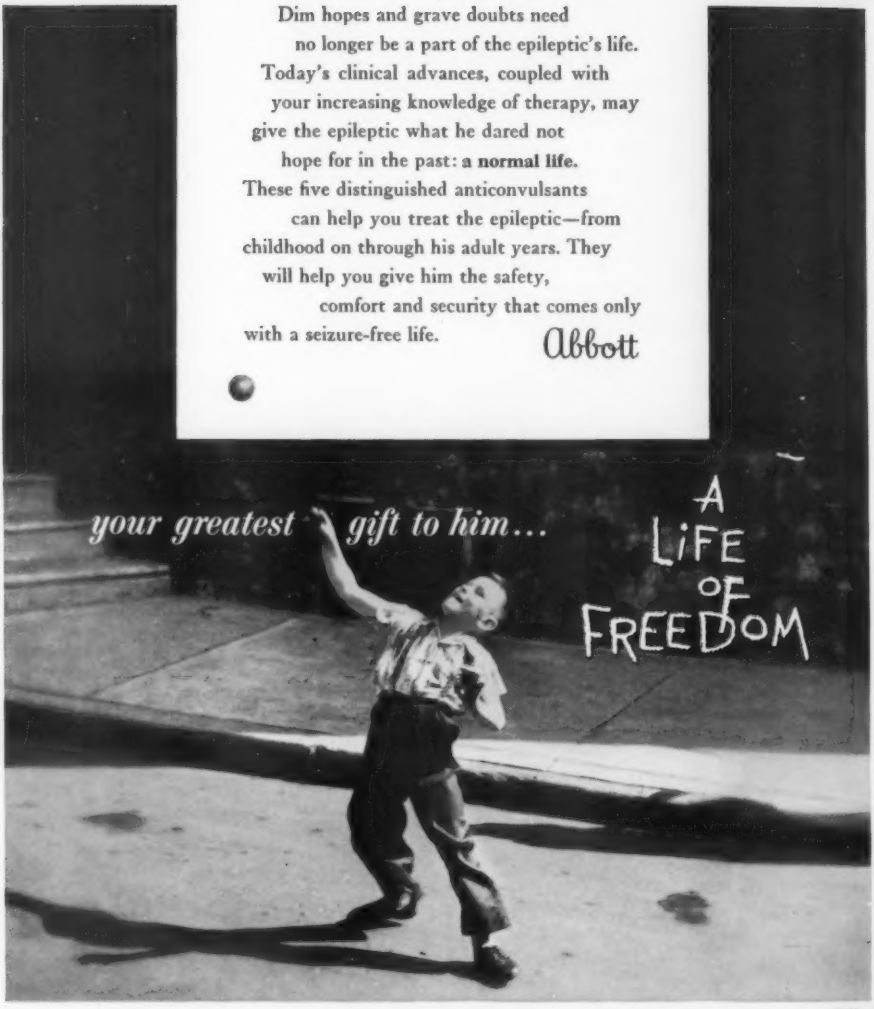

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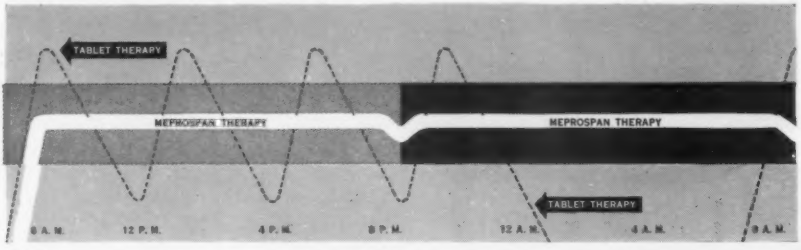

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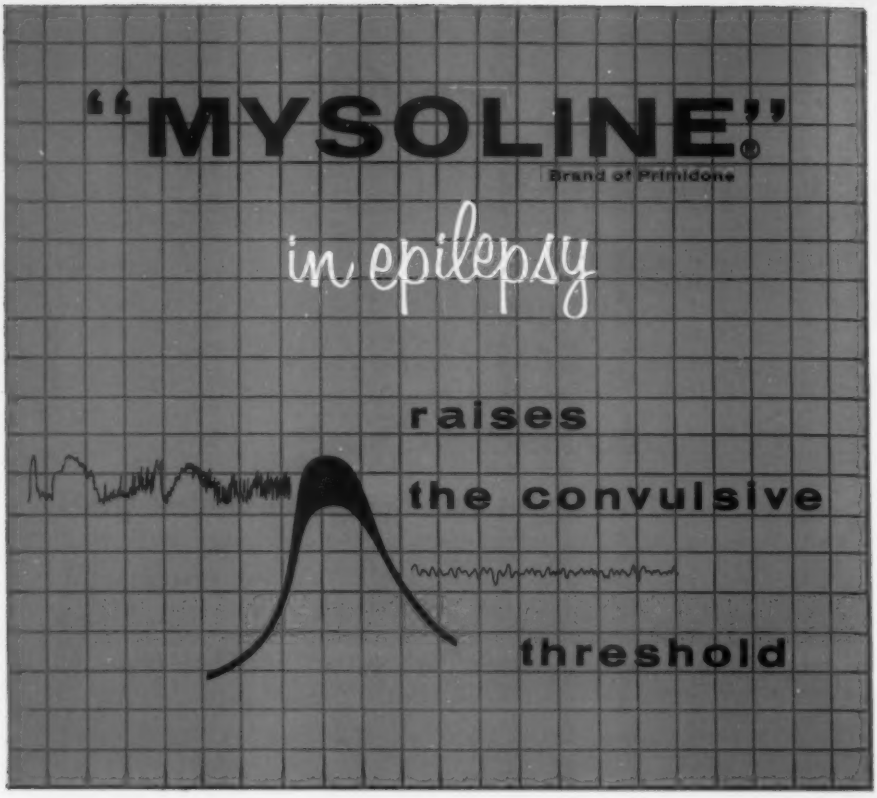

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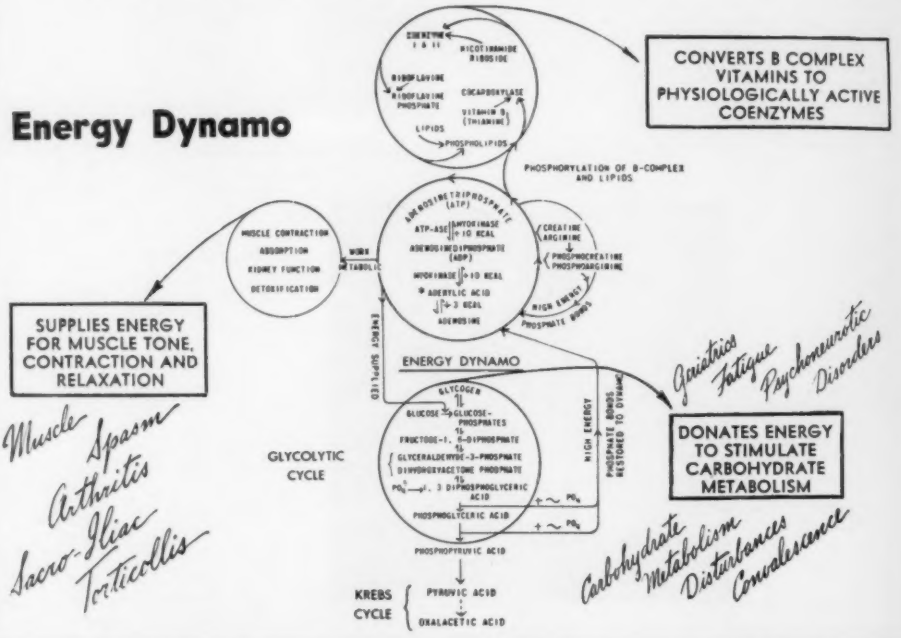

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Neurology Volume 8 • Number 5

The use of anticoagulants in cerebral thrombosis

C. Miller Fisher, M.D.

IT HAS BEEN pointed out previously[1] that, since current therapy failed to restore cerebral function after a fully developed stroke, therapeutic efforts would have to be directed primarily to the prevention of strokes. No doubt the ultimate goal in prophylaxis – the attenuation or eradication of atherosclerosis and arterial hypertension – will remain beyond our reach for some time to come, and in the meantime we must be ready to try any reasonable methods of treatment. One of the more promising of these is anticoagulant therapy, which has been recommended[1] in cerebral thrombosis with the aim of preventing the full development of infarction. The anticoagulant drug is administered either in the early stages of a progressive paralysis or at the time of the prodromal transient ischemic attacks that often herald the approach of a major stroke. If advance or worsening of the clinical picture is related to progression of the thrombotic process, the use of anticoagulant substances would have a rational basis. However, since they probably do not influence atherosclerotic deposition, it might be anticipated that, as the plaques enlarge, a time will be reached when anticoagulant action will no longer postpone cerebral ischemia.

Insofar as the prophylactic use of anticoagulant drugs is based on the recognition of either prodromal transient ischemic attacks or an early stage of the stroke process, anticoagulant therapy will be limited almost exclusively to cases of cerebral thrombosis. The other two main causes of strokes, cerebral hemorrhage and cerebral embolism, will be excluded, the first for obvious reasons and the second because in embolism the neurologic deficit usually develops abruptly without warnings; only rarely will cerebral embolism produce a stepwise or fluctuating clinical picture. In most patients cerebral thrombosis is the result of atherosclerosis, and the other causes of thrombosis (arteritis, trauma, systemic hypotension, and so on) are relatively rare.

The history of the use of anticoagulants in cerebral thrombosis is brief. Hedenius,[2] using heparin in 18 cases of cerebral thrombosis, found the results favorable in five, uncertain in ten, and insignificant in three. The clinical and therapeutic details were not given. Denber's[3] patient had three separate thrombotic episodes in less than three months; with heparin, the attacks lasted only three to 24 hours instead of one week. Rose,[4] using heparin and/or Dicumarol, found no benefit in cases in which hemiplegia had occurred. Three patients with hypertensive heart disease and also "spasm" of the cerebral arteries were given Dicumarol for long periods. After three weeks one patient had a brisk hematuria and therapy was stopped. In the other two cases further minor disturbances recurred, despite antico-

From the neurology service, Massachusetts General Hospital, and the department of neuropathology-neurology, Harvard Medical School.
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Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 23, 1957.

agulant therapy. The prothrombin concentration was maintained at 40 per cent of normal, which at present is regarded as a questionably effective level. The use of anticoagulant drugs in the treatment of transient cerebral ischemic attacks was first suggested in 1951.[5] In 1953 Fisher and Cameron[1] reported a case of basilar artery thrombosis in which heparin and Dicumarol prevented fleeting attacks of cerebral ischemia, the attacks recurring on two occasions when anticoagulants were withdrawn. The patient was placed on anticoagulant therapy for several months thereafter and remained well. Attention was drawn to the great frequency with which prodromal manifestations precede the onset of severe paralysis in cases of cerebral thrombosis. Promising results in 12 more cases treated similarly were reported at the first Princeton Conference on Cerebral Vascular Diseases.[6] Campbell[7] noted the beneficial action of anticoagulants in a 74 year old man with basilar artery thrombosis. Millikan, Siekert, and Shick[8] reported the use of anticoagulant drugs in the treatment of 26 cases of insufficiency or thrombosis within the basilar arterial system. Transient episodes ceased in the five cases of basilar insufficiency; in the cases diagnosed as thrombosis, the mortality was only 14 per cent, compared with a figure of 43 per cent in a somewhat comparable group not treated with anticoagulants. The same authors later[9] reported seven patients with manifestations of intermittent cerebral ischemia within the carotid territory, in whom Dicumarol administration abolished the attacks while patients were in the hospital. In five cases a persistent neurologic deficit was present when treatment was begun. Wright and McDevitt[10] were concerned chiefly with the prevention of embolism in cases of rheumatic heart disease, and the results in cerebral thrombosis cannot be determined from their data.

In summary, the reports to date suggest that anticoagulants prevent fleeting ischemic attacks, postpone the arrival of an impending stroke, and arrest the progressive downhill course of patients with cerebral thrombosis. However, since data pertaining to the natural course of these clinical syndromes are totally lacking at present, a reliable conclusion concerning the efficacy of anticoagulants cannot be formulated.

THE PRESENT REPORT

This paper includes 58 cases observed in the five-year period since the author began to administer anticoagulant drugs to patients suspected of having cerebral thrombosis. At the beginning, very little was known about the natural course of the neurologic deficit associated with cerebral thrombosis or the clinical picture and significance of transient ischemic attacks. Rarely was a patient referred for consultation at the stage of episodic ischemia. The history obtained from severely disabled stroke victims, however, showed clearly that transient cerebral ischemic attacks were frequently the forerunner of a major stroke. The ominous nature of these attacks was further emphasized when the first two patients with ischemic attacks, who were carefully observed personally, both developed a severe hemiplegia approximately 11 weeks after the initial examination. At about the same time, our early experience with "start and stop" anticoagulant therapy in a case of basilar artery thrombosis suggested that anticoagulants had altered the clinical course in the direction of improvement. On this basis, a preliminary trial of the routine use of anticoagulant therapy in cerebral thrombosis was undertaken, with the impression that the natural course of events was disastrous in a high proportion of cases. With the passage of time, it has become obvious that earlier fears were partly unfounded, for a neurologic deficit of vascular origin may stop advancing at any point and not all ischemic episodes signify that a stroke is imminent.

In all cases of the present group the basic pathologic process involving the cerebral arteries was thought to be a combination of cerebral atherosclerosis and superimposed thrombosis. This in turn caused ischemia of the brain, which was either temporary (transient ischemic attacks) or more prolonged and of sufficient severity to cause infarction. In most cases the period of observation was long enough to rule out such misdiagnoses as tumor, Menière's syndrome, epilepsy, and the like.

Because of the great variation in the clinical picture, it was not easy to draw up a satisfactory classification of the different types of case. The grouping of cases shown in table 1

TABLE 1

TABULATION OF CASES ACCORDING TO CLINICAL PICTURE

	Treated with Anticoagulant
1. Transient ischemic attacks (T.I.A.) with little or no residual neurologic deficit	14
2. T.I.A. with progression to a mild or moderate persistent neurologic deficit	8
3. T.I.A. following a mild or moderate stroke	7
4. Stroke-in-evolution, step-wise or gradual, with or without T.I.A.	14
5. Fully developed stroke	15
Total	58

TABLE 2

DEVELOPMENT OF THE CLINICAL PICTURE IN 125 CASES OF CEREBRAL THROMBOSIS

1. Stroke developing as a single event	21	(17%)
(a) abrupt, (hours), with or without fluctuations 14		
(b) slow, gradual (several days), with or without minor fluctuations 7		
2. Step-wise development of a stroke with or without transient ischemic attacks	23	(18%)
3. Transient ischemic attacks progressing to a persistent neurologic deficit, major or minor	53	(42%)
4. Development of a limited stroke followed by transient ischemic attacks	11	(9%)
5. Transient ischemic attacks only	17	(13%)

was finally adopted. That the categories correspond in general to the several ways in which a thrombotic stroke may develop is demonstrated in table 2, which shows the mode of evolution of the clinical picture in 125 personally examined cases of cerebral thrombosis, the majority diagnosed clinically only.

Transient ischemic attacks refer to the brief episodes of numbness, weakness, dizziness, diplopia, and impaired vision which formerly were attributed to cerebral vasospasm. Typical attacks, especially in the elderly, are usually a manifestation of cerebral atherothrombosis. Group 1 comprises cases in which such episodes were either completely reversible or nearly so, and any neurologic deficit was minimal. In group 2, ischemic episodes were recurrent but, in addition, a neurologic deficit had occurred and the attacks, although almost fully reversed, left their mark. In group 3, the patients had had a stroke of mild or moderate proportion, superimposed upon which transient ischemic attacks were occurring. Group 4 included cases in which a neurologic deficit was clearly advancing hour by hour or day by day. Usually the progression consisted of abrupt step-wise worsenings, with transient brief episodes of improvement often superimposed; in a few instances a relentless, gradually progressive deterioration took place. In group 5, the stroke was judged to be fully developed before anticoagulants were started; the deficit was so severe that worsening could not be expected.

It might be pointed out that a satisfactory explanation for the diverse clinical events encountered in these patients is for the most part not yet available, although many hypotheses have been proposed, not only for the brief, transient ischemic episode which is the hallmark of vascular occlusion due to cerebral thrombosis, but also for the intermittent attacks of worsening and the stuttering step-wise development of the full-blown stroke. It would be too great a digression here to enter into a discussion of our knowledge of cerebral atherosclerosis, the dynamics of the thrombotic process, the physiology and hydrodynamics of the cerebral circulation, and the total pathologic process underlying what is so often referred to as simply cerebral thrombosis.

Thirty-five of the patients were male, 23 were female, and their ages ranged from 30 to 72. Thirty per cent of the men and 74 per cent of the women had an elevated blood pressure (over 160/90). The incidence of involvement of the major cerebral arteries in the 58 cases was as follows: internal carotid-middle cerebral, 22; vertebral-basilar, 22; posterior cerebral, four; lateral medullary syndrome, three; and uncertain, seven. None was recognized in the anterior cerebral territory.

Anticoagulants were administered for periods varying from a few days up to four years, the mean duration of therapy being approximately six months. For long term therapy Dicumarol (bishydroxy coumarin) was usually used and the prothrombin activity, determined every seven to ten days, was maintained between 10 and 20 per cent of normal. When the neurologic deficit was advancing, as in group 4, anticoagulant action seemed urgently required and heparin was administered intravenously or subcutaneously.

In addition to the anticoagulant drugs, other therapeutic factors played a part. The patient was usually admitted to the hospital to start the anticoagulant regimen, necessitating his stopping work and even resting in bed. If anticoagulants were not a mode of therapy, it is unlikely that his daily routine would have been disturbed, at least when the complaints were minor. Cessation of smoking, the correction of cardiac failure, and the use of hypotensive drugs might well have influenced the clinical course in several cases.

Approximately one-third of the 58 patients were seen in consultation in private practice and anticoagulants were subsequently begun as recommended. In another third the referring physician had already started anticoagulants before asking for a consultation. In the remaining third (seen during the later part of the five-year period) the patient's course was first followed for a period without anticoagulants, which were given only when serious symptoms continued or evidence of a persistent stroke appeared. This procedure made it possible to compare the patient's course with and without anticoagulant drugs, and in this way a better idea of the effect of the therapy was obtained. A similar opportunity was afforded when patients who had been on anticoagulant therapy for weeks or months were observed for a period without anticoagulants and the neurologic events of the two periods compared. A modification of this pertained inadvertently when the dosage of anticoagulant proved inadequate and the prothrombin activity rose to an ineffective level.

RESULTS

Group 1. Transient ischemic attacks with little or no neurologic deficit (14 cases).

In all cases the transient ischemic attacks stopped one to ten days after effective anticoagulant levels had been reached. In no case did the attacks progress to the development of a stroke while on anticoagulant therapy for periods of three months to four years (average 15 months).

In seven cases anticoagulant therapy was discontinued after periods of one to 12 months, and in five of these cases symptoms which had stopped during treatment recurred within one week to four months. When anticoagulant therapy was started again, symptoms were once more abolished.

In six cases in which the attacks subsequently subsided on anticoagulant therapy, the patient was first observed for a period of one to six weeks without medication or treated with a variety of measures such as nicotinic acid (50 to 75 mg. three or four times a day), phenobarbital (30 mg. three times a day), papaverine (0.2 gm. three times a day) or Roniacol (50 mg. three or four times a day); during this time the attacks continued.

Group 2. Transient ischemic attacks proceeding to a mild or moderate persistent neurologic deficit (8 cases).

In seven of the eight cases transient ischemic attacks stopped within five days, and in the other case two mild attacks, possibly ischemic in type, occurred in the following three months. One patient had a temporary mild progression of the neurologic symptoms after starting therapy, but it was so slight as to be questionable. In none of the other cases was there any additional evidence of cerebrovascular disease after periods of therapy of two to 12 months.

In seven cases anticoagulant therapy was discontinued after periods of one to 12 months, and in three of these cases symptoms which had stopped during treatment recurred within one to four weeks. When anticoagulant therapy was re-instituted, the symptoms once more subsided. (In one case this was repeated on three separate occasions.) In one case there was a recurrence of symptoms when the prothrombin activity inadvertently rose to ineffective levels.

In two cases the patients were first observed before therapy was started for two to three weeks on a regimen of vasodilators (Roniacol 50 mg. three times a day, or nicotinic acid 50 to 75 mg. three times a day) and placebos without any effect on the transient ischemic attacks.

Group 3. Transient ischemic attacks following a mild or moderate stroke (7 cases).

In all seven cases transient ischemic episodes stopped within one week. Later, while still on anticoagulants, one patient for a period of a month developed numbness of one leg for

a minute or so each time he stood up after lying or sitting (this was a new symptom). In no case did a further neurologic deficit develop after periods of therapy of six months to three years.

In six cases anticoagulant therapy was discontinued after periods of one to two years, and in four of these ischemic symptoms which had stopped during treatment recurred within one week to three months; in one of the four cases a severe right hemiplegia and aphasia came on 16 days after stopping anticoagulants which had been administered for approximately 18 months; in the other three cases attacks subsided on re-instituting therapy. In another case attacks recurred twice when the prothrombin concentration rose to ineffective levels.

In three cases, before anticoagulant therapy was started, the patients were first given nicotinic acid therapy (50 mg. three or four times a day for six to ten weeks) without altering the transient ischemic attacks.

One patient, after responding favorably for two years and nine months, finally developed a progressive quadriparesis and died in coma, despite satisfactory anticoagulant therapy (case 6). Attempted withdrawal of therapy one year before death had not been tolerated.

Summary of groups 1, 2, and 3 (Table 3).

In these three groups the main feature was transient ischemic attacks, and a neurologic deficit was absent, mild, or relatively stable, a situation more or less ideal for observing the effectiveness of anticoagulant therapy in stopping transient episodes and preventing a stroke. It was perhaps to be anticipated that patients treated at the stage of transient ischemia would respond especially favorably to anticoagulant therapy. Therefore, these three groups have been combined in order to obtain a more comprehensive idea of the effect of anticoagulants in this type of case. The results in 29 cases were as follows:

Transient ischemic attacks stopped in 28 of the 29 cases. In only one case did a stroke or worsening of the neurologic picture occur and that occurred after a favorable response for almost three years. In 12 of 20 cases symptoms which had stopped during treatment recurred when anticoagulant therapy was interrupted. One of these developed a severe hemiplegia before therapy was restarted, while in the others the episodes again subsided when therapy was re-instituted. In two cases symptoms recurred when the prothrombin activity rose to ineffective levels. In 11 cases, before therapy was started, the patients were observed on a regimen of vasodilator drugs or placebos whcih were without any important effect on the transient episodes.

TABLE 3

SUMMARY OF RESULTS IN GROUPS 1, 2, AND 3 (29 CASES)

Cessation of T.I.A. (except for occasional attack)	28
Development of a stroke (after 2¾ years)	1
SPECIAL OBSERVATIONS	
Recurrence of symptoms on stopping anticoagulant	12 of 20 cases
Recurrence of symptoms when anticoagulant at ineffective levels	2
Persistence of T.I.A. during period of control observation	11

Three patients noted circulatory improvement elsewhere in the body. In one patient there was increased warmth in a limb previously cold for many months, and in two a striking decrease in the tendency to intermittent claudication was noted.

It will be noted that patients were remarkably free from transient ischemic episodes and manifestations of a stroke while receiving anticoagulants. In most of these patients, it should be emphasized, the transient attacks had been numerous and severe. Approximately half of the patients had had 20 to 100 attacks, and in the others clearly defined episodes had occurred of sufficient severity to alarm the patient. Only one of the group developed a stroke while on therapy and this occurred after clearly beneficial results for almost three years. These data suggest that anticoagulant therapy is effective in abolishing attacks and warding off an oncoming stroke. Unfortunately, however, there are no data on the natural course of events in an exactly comparable group of patients and, until these are available, an accurate appraisal of anticoagulants cannot be made.

When a comparison is made of the course of the same patients while on and off anticoagulants, there appears to be no doubt that anticoagulant therapy is beneficial. Under these circumstances, the patient himself acts

to an extent as his own control. In 20 of the 29 treated cases, anticoagulant drugs were stopped after periods of treatment varying from one to 20 months. In 12 patients (60 per cent) symptoms which had stopped during treatment reappeared when anticoagulant therapy was discontinued. Furthermore, in 11 of these 12, the transient episodes ceased once again when anticoagulant therapy was restarted. In one case this happened on three separate occasions. In the twelfth case a severe hemiplegia developed when anticoagulants were stopped. Two patients suffered a recurrence of their complaints when the prothrombin concentration rose inadvertently to ineffective levels. It is widely suggested that the recrudescence of symptoms upon withdrawal of anticoagulants is a result of the "rebound phenomenon," a transient reactive hypercoagulability of the blood; although no evidence has been adduced for this clinically, the possibility must certainly be considered.

In 11 of the 29 cases an effort was made to collect special data by first observing the patients for periods of up to ten weeks on various types of therapy such as nicotinic acid, lactose placebos, phenobarbital, or papaverine; some received no special medication. Transient episodes which had persisted in these cases ceased when anticoagulants were started. It is not easy to dismiss these results as merely the operations of chance.

That anticoagulants have a favorable effect is further supported when the above data are compared with long term observations in a large group of rather similar patients not treated with anticoagulants, an account of which will be presented below.

It is worth mentioning here that nicotinic acid, papaverine, Roniacol, and phenobarbital seemed to have no effect on the ischemic attacks and are valueless in this condition, bearing out the impression which many clinicians have formed.

Group 4. Stroke-in-evolution with or without transient ischemic attacks (14 cases). (Table 4).

Three patients developed a severe paralysis within a few days, but in the other 11 cases the results were highly satisfactory. In seven cases a steady downward course extending over periods of one to seven days was arrested and much of the neurologic deficit was finally reversed. In some patients the reversal of the clinical course was most impressive. In one case of carotid occlusion, anticoagulant therapy was withheld while the patient lost ground day by day until three of her limbs were severely paralyzed. Finally, heparin was administered intravenously and the course of events was dramatically changed. In another case the patient's course was followed until he was bedridden and unable to feed himself; when heparin was given intravenously, he improved sufficiently in three days to walk unaided. In three cases temporary minor attacks of worsening occurred in the seven-day period after anticoagulants were started, and it is possible that therapy changed a potentially grave, persistent deficit into a mild reversible one.

TABLE 4

RESULTS IN GROUP 4 (14 CASES)

Progression to a severe paralysis	3 (21%)
Satisfactory result (striking in 6 cases)	11
SPECIAL OBSERVATIONS	
Reversal of a clearly advancing stroke	7
Recurrence or worsening on stopping anticoagulant	3 of 5 cases
Recurrence or worsening when prothrombin concentration rose to ineffective levels	2

Of the three cases in which severe worsening occurred, none was given anticoagulants promptly, the dosage was too small, and the route of administration was not optimum. Two patients received depot-heparin without adequate determination of the coagulation levels of the blood. The other patient had entered the hospital following several transient attacks of right hemiplegia and aphasia, but with virtually no persistent deficit. Therapy was delayed for 48 hours, during which time the patient developed an extensive deficit. Despite adequate depression of the prothrombin activity, the hemiplegia worsened on the fifth and sixth day after starting therapy.

Anticoagulant therapy was interrupted in five of the 11 cases in which the course was favorable, and worsening was reported in three. In two other cases episodes recurred when the prothrombin activity rose to ineffective levels due to insufficient Dicumarol.

There was no significant difference in the results in basilar and carotid cases, and the

presence of hypertension did not influence the results.

Again, it is not possible to draw conclusions concerning the value of anticoagulants in this group without control studies. However, it should be stated that the author and his colleagues were especially impressed by the favorable effect of anticoagulants in patients whose condition was steadily deteriorating. The few observations on the recurrence of symptoms after stopping the anticoagulant also may indicate that the drug was exerting a beneficial action.

Group 5. Fully developed stroke. (15 cases).

In this group there were eight cases of basilar artery occlusion, five cases of middle cerebral or internal carotid occlusion, and two cases with the lateral medullary syndrome. In the basilar cases there was complete quadriplegia in all cases and coma in four. A complete hemiplegia was present in the middle cerebral cases, and the two lateral medullary syndromes were fully developed.

The results were highly unsatisfactory. Five of the basilar cases died, and paralysis remained virtually complete in two of the three survivors. In the middle cerebral cases, death occurred in two cases and in two of the three survivors the involved upper extremity remained useless and the leg served only as a pillar. The lateral medullary cases ran a most protracted course, although anticoagulants were started soon after the stroke developed.

The results did not differ from those in an untreated series. It can be concluded that a much larger number of cases followed for a long period will be necessary to determine any advantage in regard to survival or neurologic residuum.

Observations in cases not treated with anticoagulants.

During the period in which the patients described above were under treatment with anticoagulants, 37 cases were observed in which anticoagulants were not prescribed for various reasons. As more information accumulated concerning the benign course of some patients seen soon after the onset of manifestations of cerebral thrombosis, it was felt that anticoagulants could be withheld from a group of patients with relative safety in order to gain further experience with the natural clinical course of the illness; however, anticoagulants were to be given if more serious manifestations appeared. Twenty-six of the 37 cases in the non-anticoagulated group were of this class. In six further cases anticoagulant therapy had been recommended, but the patients' physicians decided not to use it. In the other five cases my colleagues kindly allowed me to follow their patients on a conservative regimen. It should be noted that the procedure of observing patients for an initial period without anticoagulants and changing to anticoagulant therapy only if worsening occurred resulted in the more favorable cases remaining in the non-anticoagulated group, the less favorable ones entering the anticoagulated group. Apart from this, the group of cases not receiving anticoagulants had about the same constitution as the anticoagulant-treated cases already described. In assessing a mode of therapy, the author is well aware of the undesirability of using for comparison a non-randomized series of cases, especially in a chronic illness with so many variable aspects. However, since clinical observations of a series of untreated cases are not available in the literature, the present group of untreated patients must be used if an appraisal, albeit limited, of the efficacy of anticoagulant therapy is to be undertaken at the present time.

There were 23 cases corresponding to groups 1, 2, and 3 and 14 cases of the group 4 type. The site of involvement was: internal carotid-middle cerebral, 19; vertebral-basilar, 15; posterior cerebral, none; and uncertain, three. Twenty-seven were men, ten were women, and their ages ranged from 30 to 70. Arterial hypertension (higher than 160/90) was found in 44 per cent of the men and 70 per cent of the women.

Groups 1, 2, and 3 (23 cases) (Table 5).

A major stroke developed in six cases, a minor stroke in two, and transient ischemic attacks persisted without evolving into a stroke in four cases. The major strokes came on within a period of one day to three months; of the minor strokes, one occurred in three months, the other in 13 months, transient episodes of ischemia having taken place in the

TABLE 5

RESULTS IN NON-ANTICOAGULATED PATIENTS

Groups 1, 2, and 3 (23 cases)	
Development of a major stroke	6
Development of a minor stroke	2
Persistence of T.I.A.	4
Group 4 (14 cases)	
Progression to a severe stroke	9

meantime. Transient ischemic attacks continued to recur for over a year in two cases; of the other two patients, one had a single brief attack of aphasia after three months, the second had two attacks of transient monocular blindness in the following six months.

In 11 cases ischemic attacks ceased spontaneously. Four of these patients stopped smoking cigarettes, a factor which the author suspects is of great etiologic importance. Another patient had developed a mild hemiparesis the day before examination, following which there were no further ischemic attacks; he, too stopped smoking cigarettes. In the remainder, attacks ceased without any special measures. One of these patients had had two 15-minute attacks of aphasia and right hemiparesis; although he continued to smoke, drink, eat, and work, all in excess, there was no recurrence in one year. Another patient had 25 to 30 attacks of numbness of the right side of the body in a period of a week and then no more in the next two years.

Group 4 (14 cases).

A severe stroke developed in nine cases, of which seven occurred within two weeks; seven of the nine died. (In all cases the neurologic deficit was mild or moderate when the patient was first seen). In four of the five cases running a favorable course, there had been a major neurologic episode involving the brainstem bilaterally and, although worsening was anticipated since the stroke fell far short of the picture of total basilar occlusion, no progression occurred. Such cases illustrate the principal difficulty encountered in the management of cases of cerebral thrombosis – the problem of determining where the patient stands in the course of his total stroke when he is first examined. In unilateral brainstem infarction the prognosis for recovery is often good, whereas bilateral involvement is usually regarded with the greatest concern; yet the four patients cited have suffered no advancement in their illness over periods as long as two and one-half years.

Comparison of the anticoagulated and non-anticoagulated groups shows that the former group fared much better; however, because of the manner of selection of cases, great care must be exercised in drawing conclusions. The author feels, nonetheless, that this comparison of the two groups, especially when taken in conjunction with the special observations in the treated group (that is, the clinical course on and off anticoagulants), indicates that the use of anticoagulants is an extremely promising mode of therapy and that it will prove to be useful in the delaying action against cerebral thrombosis.

DISCUSSION

The main conclusions regarding the efficacy of anticoagulant therapy have already been discussed in the preceding sections and there is little to add here on that subject.

It is obvious that the efficacy of anticoagulant therapy has not been clearly proved. At present, the most that one can say is that the results are suggestive and that this type of therapy offers greater promise than any other used by the author. There is great need of a large-scale systematic study of many more cases, using identical methods for selection and treatment. This is now being undertaken and we hope to be able to present these results in the future. Until such time as these data become available, the medical profession must defer final judgment on this method of medication. However, if faced with the problem of treating cases of cerebral thrombosis, anticoagulant therapy deserves a trial and can probably be used with reasonable safety under the circumstances described below.

In regard to the length of time that anticoagulant therapy should be maintained, no hard and fast rules have yet been laid down. The author is inclined at present to stop the anticoagulant after a six-month period and to start therapy again only if further trouble occurs. In most cases symptoms did not recur after a six-month period on an anticoagulant and some of these have been followed up to five years; however, in four of the cases re-

ported, symptoms reappeared when the drug was withdrawn after one to two years.

Some remarks will now be made concerning the selection of cases for anticoagulant therapy, and this will be followed by a consideration of several aspects of the use of anticoagulant drugs which warrant further attention, namely, the complications of anticoagulant therapy, the recognition of transient ischemic attacks, and, finally, the mechanism of action of the anticoagulants.

Selection of cases for anticoagulant therapy.

It is assumed here that cerebral thrombosis has been established as the diagnosis. First of all, it would seem from the data relating to group 5 that therapy is relatively useless if begun when the stroke is full blown and, therefore, our efforts should be directed to patients at an earlier stage of the illness. Yet it is equally true that many cases with transient ischemic attacks or even a relatively advanced neurologic deficit will fare well without anticoagulant medication. Hence several questions must be posed: Is it possible beforehand to distinguish the cases destined to do well without anticoagulant drugs from those whose course will be unsatisfactory? Should one select for therapy only those patients who have a well-defined neurologic deficit, or is it advisable to use anticoagulants on the mildest of indications? So far, there are no satisfactory answers to these questions and the following tentative rules from the author's experience are presented as a guide, especially for those who, in order to spare their patients the nuisance and expense of anticoagulant therapy, are prepared to take a risk and withhold therapy until the natural course of the patient's illness has been established as unfavorable.

1). This mode of therapy has a rational basis when transient ischemic attacks are recurring with increasing frequency, lasting longer, or reversing themselves less completely, that is, a neurologic deficit is accumulating. The corollary to this is that, when ischemic attacks are becoming less frequent or lasting a shorter time, the urgency of treatment of any kind is reduced. The next attack may be the last. When ischemic attacks appearing for the first time recur at frequent intervals, for example, every few minutes or every hour, heparin should be administered intravenously immediately.

There is a group of cases in which a mild sensory defect persists from the time of the first episode, superimposed upon which repeated attacks of temporary numbness or other paresthesias occur. These may occur for weeks or months and gradually fade away without special therapy. It is sometimes difficult in these patients with a mild persistent numbness to know whether an episodic intensification of symptoms represents attacks of recurrent ischemia or simply a fluctuation in the patient's awareness of the paresthesias. Anxiety seems to be an aggravating factor in this respect. The same difficulty is encountered in interpreting the occurrence of scintillating scotomata in association with a persistent homonymous hemianopia.

2) Therapy would also seem to be indicated when a stroke is developing in a step-wise or gradual manner over a period of hours or days (group 4).

3) When a patient is seen after a single brief attack which has cleared completely, the question arises: Is it safe to wait and see what happens next without anticoagulant therapy? Of course, cerebral embolism must be suspected and a source of emboli in heart or lung must be sought. If the diagnosis of embolism is established, prolonged anticoagulant therapy administered with the aim of preventing further embolism seems to be justified. (Cerebral hemorrhage is not a cause of evanescent strokes and, therefore, need not be considered). In the case of cerebral thrombosis, uncertainty exists as to the wisest course, for, although in the great majority of such instances anticoagulants can be withheld safely, we have all seen cases in which only one warning episode preceded the sudden development of a severe disability. One may argue that, considering the difficulties and hazards of anticoagulant therapy, one probably should withhold therapy in these cases, despite the risk. However, arrangements should be made to give heparin intravenously as an emergency measure should a non-remitting neurologic deficit develop. The patient should be carefully observed, and it is advisable to awaken him at least twice during the night for seven

to ten days to insure that he can respond and has not developed any symptoms of focal brain disease, in which case heparin could be administered intravenously, 50 mg. every four hours.

4) When a single neurologic episode has occurred leaving the patient with a persisting deficit which is of lesser severity than one would expect from a total insult to the territory involved (this might be termed a partial or limited stroke), one must suspect that additional trouble lies in store. In the carotid territory a total deficit will consist of a complete hemiplegia and, if the dominant hemisphere is involved, a total aphasia or severe dysphasia will also occur. Therefore, if only a monoplegia or a mild dysphasia is present, further insult is to be expected. In the basilar territory the first, or mildest, persistent fragment of a stroke may take many different forms, for example, cerebellar ataxia, dysphagia, dysarthria, weakness of the limbs of one or both sides, diplopia, paralysis of gaze, impaired vision, and confusion, and progression to hemiplegia or quadriplegia with coma must be feared. In an attempt at exercising greater selectivity in the choice of patients, it is probably wise to withhold anticoagulant therapy and await further developments but remain prepared to administer heparin as an emergency measure should any worsening occur. Awakening and checking the patient is a precautionary measure. Such great conservatism has its risk and one might argue that it would be justifiable to administer an anticoagulant forthwith on the assumption that, while no harm would be done, great benefit might accrue.

Reference has previously been made to the crucial question in cerebral thrombosis: Where in the natural history of his stroke does the patient stand when he is first examined? Probably every physician has been embarrassed to find that what appeared to be a rather innocent-appearing mild stroke has turned abruptly into a major catastrophe. It should be emphasized that disaster resulting from cerebral thrombosis has not occurred in any of the patients treated early with anticoagulants, and therein lies all the more justification for not delaying therapy until worsening occurs.

There may be an additional reason for starting anticoagulant therapy before waiting for conclusive evidence that progression has occurred, and this relates to our impression that, after giving an anticoagulant for some weeks and then withdrawing it gradually, symptoms, if they recur, begin in a mild fashion rather than precipitously. If this is correct, early therapy for six weeks would be a satisfactory way of tiding the patient over the most uncertain period. This matter is not settled, however, and some clinicians have claimed without evidence that the risk of thrombosis is greater during the withdrawal period than at any other time ("rebound phenomenon").

5) From the observations in groups 4 and 5, it is obvious that the later in the course of the illness anticoagulant therapy is started, the more need there is to achieve an effective anticoagulant level as quickly as possible. In basilar artery occlusion particularly, the downward course is likely to be rapid, and within a few hours a relatively benign motor or sensory deficit can turn into an alarming degree of paralysis. In an emergency, heparin is given intravenously every four hours day and night until the concomitantly administered Dicumarol has reduced prothrombin activity to desirable levels. It is suspected that the transitory high levels of anticoagulation achieved by the intravenous route result in a more satisfactory concentration of heparin adjacent to the thrombus in the cul-de-sac of the occluded arterial segment, a site possibly difficult for circulating anticoagulant to reach.

The favorable clinical course of the neurologic illness after cessation of smoking deserves further comment. In one case attacks of numbness of the face and hand, which had been occurring several times daily for weeks, stopped from the moment the patient gave up cigarette smoking. In another case attacks diminished from about 20 per day to two or three per day within 24 hours of stopping smoking. Other patients with repeated cerebral attacks over a period of months or years have been symptom-free up to three years since abstaining. In view of the recent demonstration that Buerger's disease may not be a separate entity but rather a manifestation of premature atherosclerosis, and since cessation of smoking was held to be unquestionably beneficial in cases of Buerger's disease, one might use this clinical observation to suggest

that smoking aggravates atherothrombosis in some way. This would be in agreement with our present observations on the cerebrovascular effects of smoking, and it must be remembered that the nervous system is a far more sensitive indicator of transient ischemia than heart or limbs. The corollary to all this is that nonsmokers who develop transient ischemic attacks might be expected to fare worse than smokers with a similar illness who then give up tobacco.

Anticoagulant therapy is not used at present when a stroke has become "fully developed." The term "fully developed" is not easy to define, for it varies with the territory affected. For example, anticoagulants appear not to be indicated in cases showing a classic lateral medullary syndrome. The same is true of occlusion of the posterior cerebral artery in which a full hemianopia exists. The same rule would apply in the case of the individual major cerebellar arteries, but it is extremely difficult to separate their syndromes from the manifestation of basilar artery disease. When there is only evidence of unilateral pontine involvement which is stationary, therapy can be delayed. In the middle cerebral territory, anything less than a complete hemiplegia is viewed with the expectancy in mind that worsening is in the offing. However, even when a neurologic deficit following a stroke appears to be maximal, careful observations have shown that fluctuations may still be occurring and a deficit worse than the apparent maximum will finally be reached. When fluctuations are detected, anticoagulant therapy may be tried. There is also the possibility that anticoagulants prevent a thrombus from propagating to block a more proximal branch of the main vessel, but we have made no observations on this point.

Complications of anticoagulant therapy in our series of cases.

Of the 58 patients reported herein who were given anticoagulants, six developed complications as follows: hematuria, three; bleeding from a duodenal ulcer, one; hemorrhage into the abdominal wall, two. Only the last two were of a serious nature and both patients were in a precarious state for many hours due to shock.

Special circumstances to which the episodes of bleeding might be attributed were present in five of the six cases, namely: gross overdosage due to inexperience, two; faulty laboratory technic, one; patient irresponsibility due to alcoholism, one; failure to have regular prothrombin determinations (none for two months), one. Only in the case of the bleeding duodenal ulcer did the complication occur while the patient was under adequate anticoagulant control, and the patient had had a gastrointestinal hemorrhage in the past long before anticoagulant therapy was started. This incidence of complications (10 per cent) is low, considering the fact that 22 of the cases received therapy for more than six months. It is justifiable to conclude that long term anticoagulant therapy is safe, provided supervision is adequate and reliable prothrombin determinations are carried out every seven to ten days. As already mentioned, the desirable prothrombin concentration is 10 to 15 per cent and only when levels of approximately 2 per cent are reached is bleeding liable to occur. Patients with an unexplained significant prolongation of the clotting time due to Dicumarol administration were not recognized. It might be mentioned that two patients not included here, who were receiving long term anticoagulant therapy because of repeated small hypertensive thrombotic strokes, developed fatal intracerebral hemorrhages, one of them, at least, at a time when the prothrombin concentration was at a desirable level (8 per cent). Although these hemorrhages might have occurred regardless of therapy, since the patients had a severe degree of hypertension, the anticoagulant drug must be held responsible until proved otherwise. Hypertension of moderate degree, while not a contraindication to anticoagulant therapy, should make the physician doubly cautious. In some cases antihypertensive agents may be combined with the anticoagulant therapy, but the former should not be used for a period of two to three weeks after a thrombotic stroke.

The question often arises whether anticoagulants cause bleeding into areas of recent infarction. In my experience, anticoagulant drugs have not resulted in hemorrhage into a pale infarct and, furthermore, pathologic observations in six cases showed that hemor-

rhagic infarction was not aggravated. These observations will be reported in detail later.

Transient ischemic attacks — clinical picture — differential diagnosis.

Since transient ischemic episodes are among the earliest manifestations of cerebral thrombosis and one of the chief criteria for the selection of cases suitable for anticoagulant therapy, their principal characteristics will now be described in some detail.

Transient ischemic attacks can occur by themselves or they may precede, accompany, or follow the development of a stroke. As already mentioned, it is impossible to predict accurately in which cases a neurologic deficit will occur (or worsen, if one is already present). There would seem to be no doubt that these brief episodes are ischemic in nature and not primarily a seizure phenomenon. They are linked almost exclusively to occlusive atherothrombotic vascular disease, if one sets aside the cerebral episodes associated with migraine, failure of the systemic blood pressure, and possibly polycythemia. Corresponding to the higher incidence of atherosclerosis in males and in association with hypertension, two-thirds of all patients in the present series were men and two-thirds had arterial hypertension. Until the possibility arose of altering the course of cerebral thrombosis by the administration of anticoagulants, little attention was paid to these attacks and as yet no thorough description of them has appeared in the literature.

Transient ischemic attacks can arise in association with thrombosis of any cerebral artery, deep or superficial, for example, common carotid, internal carotid, middle cerebral, anterior cerebral, vertebral, basilar, posterior cerebral, and the cerebellar arteries and the penetrating branches to the deep structures of the basal ganglia and brainstem. If the posterior cerebral arteries are regarded as part of the vertebral-basilar system, ischemic episodes are slightly more common in that system than in the carotid system. The neurologic features of the transient episode indicate the territory or artery involved and are fragments borrowed from the stroke which often is approaching.

The clinical picture in the carotid system may consist of unilateral weakness or numbness (of face, hand, leg, or part thereof, on the side of the body opposite to the lesion), dysphasia (when the dominant hemisphere is affected), confusion, veering, monocular blurring of vision or blindness, scintillating scotomata, headache, and possibly focal epileptic seizures.

In the vertebral-basilar system the picture is extremely diverse, since so much motor and sensory traffic is sustained by the blood carried in the basilar artery. Occurring in the most varied combinations, the following may be recognized: weakness of part or all of one side of the body or both sides, or crossed weakness, numbness of part or all of one side or both sides, crossed weakness and numbness (weakness on one side, numbness on the other), dizziness, diplopia (vertical or horizontal), dark vision, blurred vision, tunnel vision, partial or complete blindness, scintillating scotomata, pupillary change, ptosis, paralysis of gaze, dysarthria, speechlessness, dysphagia, staggering gait, veering, headache, noise or pounding in the ear or in the head, head or face pain, peculiar head sensations, vomiting, hiccoughing, memory lapses, confused behavior, temporal lobe seizures (rare), drowsiness, unconsciousness (rare), impaired hearing, deafness, a feeling of movement or twitching (rare), sweating, and facial redness.

If a persistent neurologic deficit is not present at the time of the transient ischemic attacks, it may appear at any time. In either case, the neurologic signs will correspond to the subjective complaints and will be of great assistance in localizing the site of the lesion. Signs of involvement of the carotid territory include: contralateral paralysis and cortical sensory loss, dysphasia, homonymous hemianopia, agnosias and apraxias, monocular blindness, loss of pulsation in the carotid artery in the neck or pharynx, reduced pressure in the central retinal artery, and a contralateral cranial bruit. Disease of the basilar system will be indicated by bilateral impairment of the motor or sensory long tracts, peripheral cranial nerve disturbances (limitation or paralysis of ocular movement, sensory loss over the face, weakness of masseter muscle, facial palsy, deafness, tinnitus, dizziness and nystagmus, deviation of palate, paralysis of vocal cord, or weakness of the tongue), cerebellar ataxia, conjugate

gaze palsies, skew deviation, cortical blindness, Horner's syndrome, choreoathetosis, rhythmic myoclonus, or "rubral" tumor.

It is not always easy to identify the territory affected. However, the occurrence of receptive or sensory dysphasia always points to the carotid system, as does monocular blindness. The hallmarks of vertebral-basilar involvement are a) *bilateral* weakness and/or numbness, that is, a disturbance of the long motor or sensory *tracts* bilaterally; b) peripheral cranial nerve involvement; c) whirling dizziness; and d) cerebellar ataxia. Dizziness as a manifestation of an attack may be difficult to analyze. If the patient is absolutely free of vertigo between attacks, the episode of dizziness probably reflects a bout of ischemia, but if postural dizziness occurs related to turning of the head in between attacks, it is more likely that some persistent damage to the vestibular system has occurred, in which case temporary worsening of symptoms may reflect a postural change rather than a recurrence of ischemia.

Unilateral weakness and unilateral numbness as isolated phenomena may be difficult to localize, since they occur in both carotid and basilar occlusion. Even an isolated unilateral paralysis of an arm or a leg can occur in basilar artery disease and must not always be taken as an indication of a supratentorial lesion. Perioral numbness is not infrequently a complaint, and often the patient is not certain whether it is equally bilateral, bilateral with unilateral preponderance, or mostly unilateral with spread slightly to the other side of the midline.

The following are rare or unknown in ischemic attacks: unconsciousness, convulsive movements, fecal or urinary incontinence, facial pallor, formed hallucinations, and the manifestations of temporal lobe seizures. Pain in a limb has not occurred, but facial pain has been encountered in ischemic attacks.

An ischemic attack may involve many cerebral structures and produce a host of neurologic manifestations, as in some dramatic cases of basilar artery disease when total paralysis of face, arms, and legs occurs along with dizziness, diplopia, blindness, dysphagia, aphasia, and numbness of one or other part. In other cases the ischemic attack may be highly localized and limited to the slightest degree of diplopia or to discrete attacks of numbness involving one side of one lip or one thumb only. This might be interpreted to mean that blood flow can be compromised in many branches of a main trunk or in a small twig.

Transient ischemic attacks may last from a few seconds up to several hours, the most common duration being a few seconds up to five or ten minutes; sensations that come and go in a second are usually not ischemic manifestations, but a few patients have described flashes of numbness between longer-lasting episodes. It is uncommon for recurrent discrete attacks to last more than 30 minutes. There may be only a few attacks or several hundreds. A stroke may ensue after the second one or be postponed until hundreds have occurred over a period of weeks or months. Not infrequently the attacks gradually cease and no important paralysis occurs. It is my impression that transient symptoms which appear on awakening from sleep are especially liable to be followed by a stroke. The attacks may all take approximately the same pattern, or they may vary considerably in detail although maintaining the same basic pattern. For example, weakness or numbness may involve fingers and face in some episodes and only fingers in others, or dizziness may occur alone in some attacks, while in others diplopia is added to the picture. In basilar artery disease each side of the body may be affected alternately. All the involved parts may be affected simultaneously, or a definite march or spread from one region to another can occur in a period of ten to 60 seconds, for example, numbness may spread from the hand to the face, or the reverse. Each attack may cease abruptly or fade gradually.

The onset of attacks in some cases is clearly related to standing up or leaping up after lying or sitting. Yet tilting such patients on a tilt table until the systolic blood pressure falls to 100 or 90, or even 80 mm. Hg, usually fails to bring on an attack. Thus, there is an apparent discrepancy between clinical and laboratory observations. In one case that has come to our attention, the patient, who had been complaining of attacks of numbness of the left side of the body (indicating an impaired circulation to the right cerebral hemi-

sphere), was subjected to a laboratory procedure which was followed by temporary vascular collapse. On regaining consciousness, the patient was found to have a *right* hemiplegia, aphasia, a blue, cold, pulseless right leg, and evidence of myocardial infarction. The only parts still functioning were the left arm and leg.

Attacks are likely to occur when the patient is up and around rather than lying down, but in many cases the episodes occur regardless of position. They are especially frequent shortly after arising in the morning or during breakfast. They have been encountered in relation to exercise, exertion, emotional outbursts of anger or joy, and during bouts of coughing.

Ophthalmoscopic observations of the retinal vessels made during episodes of transient monocular blindness show arrest of the blood flow in the retinal arteries and breaking up of the venous column to form the well known box-car pattern. This could well indicate that, in ischemic attacks elsewhere, a temporary complete or relatively complete cessation of blood flow occurs locally.

Differential diagnosis of transient ischemic attacks.

The following conditions must be differentiated from recurrent transient ischemic attacks: focal cerebral (epileptic) seizures, Menière's syndrome, paralytic migraine, Stokes-Adams attacks, carotid sinus reaction, akinetic falling spells of the aged, and cerebral embolism. On rare occasions ischemic episodes may be confused with tussive syncope, multiple sclerosis, cataplexy with narcolepsy, the distress of hiatus hernia, cervical disk disease, unusual subjective symptoms of angina pectoris, severe postural hypotension, transient global amnesia, recurrent pulmonary embolism, hemangioma of the brainstem, and assorted ill-defined conditions. It is not always an easy matter to establish the correct diagnosis, and, to add to the difficulty, the patient, in his fear that a stroke is in the offing, may complicate the picture by reporting all sorts of vague sensations. In cases of the group 4 type, in which a single neurologic episode has occurred or a neurologic deficit has appeared gradually, that is, the factor of recurrence does not assist in the diagnosis, the problem is even more complex, for cerebral embolism, a small cerebral hemorrhage, cerebral tumor, multiple sclerosis, and subdural hematoma can each produce a picture simulating cerebral thrombosis.

Cerebral seizures. Since it would entail consideration of the many different topographic seizure patterns, a detailed discussion will not be undertaken here. Insofar as both ischemic episodes and seizures are transient, brief, recurrent neurologic disturbances, the problem of differentiating one from the other is constantly arising; especially is this so when the attack consists of visual symptoms or numbness. Motor phenomena are probably less equivocal; judging from personal experience, it appears that frank motor convulsions are extremely rare in ischemic attacks. This finding is surprising, since seizures are often held to be a frequent sequel of cerebral anoxia and cerebral ischemia. Occasionally, in an ischemic attack, the muscles of the affected part may tremble mildly or there is a feeling of movement, distortion, or drawing, but no patient has described jerking or twitching. Usually the affected limb simply becomes weak. On the other hand, it must be extremely rare that temporary paralysis of a limb or of one side of the body constitutes the only manifestation of a cerebral seizure.

"Unconsciousness," although rare in transient ischemic episodes, occasionally occurs in basilar artery attacks. In the great majority of ischemic attacks the patient remains alert. Incontinence of bowel and bladder, tongue biting, frothing, cyanosis, and residual sleepiness or muscular soreness do not occur or are extremely rare in ischemic episodes. Blanching of the facies, often seen in epilepsy, is rarely encountered in vascular crises, but flushing can occur. Sensory phenomena such as numbness or scintillating scotomata produced by transient ischemia may resemble sensory seizures very closely. In making a differentiation, it is well to depend on associated phenomena. For example, if a bout of numbness of the hand and foot is combined with diplopia or spinning dizziness, the attack is probably ischemic, since diplopia and spinning dizziness are rare or do not occur at all in epileptic seizures. The absence of an epileptic "march" is

not decisive, for in some transient ischemic episodes a definite spread from one part to another occurs. If the sensory disturbance progresses promptly to unconsciousness or jerking, even if only in some of the attacks, the diagnosis of seizures is most likely. In one of our cases of basilar artery thrombosis, the patient was subject to spells in which she perceived an unpleasant pungent odor, but this was the closest approach to temporal lobe seizures. The electroencephalogram may be useful in differentiation, insofar as vascular attacks arising in the brainstem and internal capsule might be expected to occasion no change in the cerebral electrical pattern, while the presence of a cortical seizure-type discharge would indicate that seizures had to be considered seriously. It is recommended that one rely chiefly on a careful analysis of the patient's complaints and use the electroencephalogram only as an ancillary measure. In especially ambiguous cases, a therapeutic trial of phenobarbital or Dilantin might be helpful.

Menière's syndrome. Dizziness in the form of spontaneous recurrent attacks or in relation to postural changes is one of the commonest symptoms of occlusion within the vertebral-basilar system. So far, it has not been possible to distinguish the dizziness of vascular origin from that associated with Menière's syndrome or primary labyrinthitis, and in making a diagnosis it is necessary to depend on the presence or absence of certain other signs. It is a simple matter to decide that the dizziness is of central origin when there are other evidences of brainstem involvement by history or on neurologic examination: diplopia, numbness, weakness, dysphagia, a Horner's syndrome, cerebellar ataxia, vertical nystagmus, persistent horizontal nystagmus, and so on. On the other hand, one can say that it must be extremely rare for recurrent dizziness, tinnitus, and chronic deafness to be the only symptoms of an ischemic attack (of the type under discussion in this paper) and, therefore, the presence of this triad in isolation is almost certain evidence of the Menière syndrome. However, we have encountered several cases in which proved vertebral-basilar disease featured the rather abrupt development of dizziness, deafness, and tinnitus over a period of a few days, with only slight evidence of brainstem involvement in the early part of the course. In these cases tinnitus has not been prominent, whereas the deafness tended to be severe.

Most difficult of solution are cases in which attacks of dizziness are the sole complaint, and in the elderly one must suspect brainstem vascular disease. To establish a diagnosis, it is often necessary to observe the patient for a period of time, awaiting further developments such as diplopia or numbness. Marked nystagmus persisting throughout the clear periods between attacks of dizziness suggests a brainstem disturbance. A red glass or some other more refined test for diplopia may be necessary to detect a slight oculomotor imbalance.

It must be kept in mind also that basilar artery disease and Menière's syndrome may co-exist since neither disorder is infrequent. Audiometric and vestibular tests by themselves are rarely crucial in establishing the diagnosis, and it is preferable to rely primarily on a careful assessment of the clinical details.

Migraine. Only occasionally will migraine and transient ischemic attacks need to be differentiated. If one subscribed to the idea that ischemic episodes are due to vasomotor changes, it might have been anticipated that patients with ischemic attacks would frequently give a history of migraine in their earlier years, but in the present series of cases the combination has been surprisingly rare.

Headache frequently accompanies cerebral thrombosis, but it would be unusual to confuse this with the periodic headache of ordinary migraine-without-aura, unless the patient's era of migraine happened to extend into the period during which serious cerebrovascular disease was evolving. However, it is not uncommon in transient ischemic attacks for headache to be combined with scintillating scotomata or numbness, and when a history of migraine is obtained, it might be difficult to decide between a recrudescence of migraine-with-aura and the appearance for the first time of ischemic attacks. Occasionally migraine-with-aura recurs after a headache-free interval of 15 to 20 years. Several cases have been encountered in which migraine had been diagnosed erroneously in middle-aged patients who were developing occlusion of the pos-

terior cerebral artery, to the accompaniment of headache and unformed visual hallucinations such as scintillating spots. The vexatious possibility of migrainous aura without headache is frequently raised in patients with one, or even a few, brief transient attacks of numbness or scintillation, but this diagnosis would be justified only if there was a close link with previous migrainous phenomena of a similar form.

Stokes-Adams attacks (and hypersensitivity of the carotid sinus reflex) bear only a superficial resemblance to transient ischemic attacks, but must be considered when a patient is subject to collapsing spells for which no adequate description is available. The demonstration of carotid sinus hypersensitivity does not necessarily mean that the cause of the patient's attacks has been discovered, for it must be remembered that in the elderly the sinus region is not infrequently sensitive to massage and the two disorders may co-exist. It is probably safe to assert that cardiac asystole will not regularly produce recurrent focal neurologic manifestations (numbness, weakness, diplopia, and so on), whereas transient ischemic attacks are much more likely to produce clear focal signs than they are to lead only to collapse and confusion. A careful minute-by-minute description of the attack will usually allow the correct diagnosis to be reached. If cardiac arrest can be detected during an attack, the diagnosis will pose no problem.

Akinetic falling spells of the aged. From time to time, cases are seen in which elderly patients fall unconscious or semicounscious without convulsive movements, color change, or alteration in pulse, blood pressure, and respiration. After a minute or two, the victim returns to his usual status. These attacks appear to be in the nature of an unusual seizure although their exact nosologic status is not clear. The electroencephalogram may be normal or average for the patient's age.

Cerebral embolism. This diagnosis is frequently suggested as an explanation for recurrent cerebrovascular episodes. Generally speaking, emboli are destructive of brain tissue and this combined with the unlikelihood that several successive emboli would enter the same arterial branch or same twig make it clinically impossible to explain *recurrent transient attacks all of the same pattern* on the basis of cerebral embolism (as one usually understands embolism). On the other hand, multiple brief episodes affecting different parts of the brain might well be explained by multiple small cerebral emboli (bland, infected, marantic or tumor). Since this paper is concerned chiefly with *recurrent* episodes confined to one vascular territory, multiple embolism will be considered no further.

The mechanism of action of anticoagulant drugs.

So far, no reference has been made to the mechanism by which anticoagulant drugs arrest the clinical course of cerebral thrombosis and abolish transient ischemic attacks. Transient ischemic episodes have in the past been attributed to cerebral vasospasm or to a primary failure of the systemic blood pressure, especially on arising in the morning or after eating. An important, newly demonstrated characteristic of these attacks is their prevention by anticoagulant drugs, and it is not easy to reconcile this behavior with the concept of vasospasm or the failure of the systemic circulation. It has been suggested, on the basis of pure speculation, that the anticoagulants, Dicumarol and heparin, act via their mild vasodilator property. However, in our experience, these drugs do not have an immediate action, but their effect on transient ischemic attacks is delayed at least until the full anticoagulant effect has been attained or the prothrombin activity appropriately reduced. This would argue strongly against the drugs having a direct dilator effect on the arterial wall. The same conclusion is suggested by the recurrence of ischemic attacks during long term therapy when the prothrombin activity has risen, despite a constant dosage of Dicumarol. In six of the 43 cases in groups 1, 2, 3, and 4, attacks continued to occur for two, two, three, three, seven, and ten days, respectively, after anticoagulant levels were well within the effective range (coagulation time three times the control, prothrombin activity 10 to 29 per cent), and this would point to the probability that the anticoagulant drug sets in action some process which, after a period of time varying from case to case, changes the physical basis for the attacks. One might speculate that, during this period

of delayed action, recent thrombus blocking the remaining lumen of the main vessel, or the exit of a branch, or the entrance of a collateral channel might be undergoing dissolution. However, our knowledge of the minute details of the anatomic substrate underlying ischemic attacks is so scanty that speculation is liable to be fruitless. Another possibility is that anticoagulants favorably affect the flow of blood in small collateral channels, serving to maintain an adequate supply to the compromised territory. The pathologic findings in case 4 suggest that anticoagulant therapy over a longer period might allow organization and endothelization of an existing clot so that progressive or advancing thrombosis is arrested and does not recur when the drug is withdrawn.

No striking advantage of heparin over Dicumarol in abolishing transient ischemic attacks has been noted. Of course, when an anticoagulant effect is urgently required, heparin must be used.

"Anticoagulation" is a relative matter and, judging from these preliminary data, the use of anticoagulant drugs appears to lessen the tendency to intravascular thrombus formation without providing absolute protection. This measure of relative protection can be overcome whenever particularly potent factors tending to thrombosis exist locally. Since protection is only relative, it is remarkable to find that virtually none of the cases reported herein showed overt progression of their illness while under adequate long-term therapy. Anticoagulants, of course, do not (as fas as is known) arrest the development of atherosclerosis, and sooner or later the progressive deposition of lipid can be expected to annul the anticoagulant effect, as occurred in case 6. However, this is not necessarily so, as is shown by the pathologic findings in one of the earlier cases (case 4). The patient, a woman, had basilar artery disease and was totally paralyzed immediately before anticoagulation was begun. Recovery was satisfactory and anticoagulant therapy was maintained for six months. Thereafter, the patient ran an uneventful course until she died suddenly of a myocardial infarction four years later. At autopsy, the basilar artery was found to be totally occluded in its lower portion by firm white tissue, obviously an ancient organized thrombus. A small softening lay in the right side of the basis pontis. It could be concluded that anticoagulant therapy arrested the local thrombotic process and possibly staved off disaster until collateral blood flow to the basilar territory became established. This may mean that anticoagulants serve to tide the patient over a crucial period and thereafter therapy can be dispensed with, at least temporarily.

SUMMARY

Anticoagulant drugs have been administered to 58 patients with symptoms and signs of the various stages of cerebral thrombosis due to atherosclerosis. The data suggest that anticoagulant therapy abolishes transient ischemic attacks and prevents or postpones the arrival of a threatening stroke. When used in the early stage of a progressively evolving stroke due to cerebral thrombosis, the downhill course appears to be satisfactorily arrested and reversed. Patients observed for periods both on and off anticoagulants fared better while receiving anticoagulants. A group of 37 cases rather comparable to the anticoagulant group were observed without anticoagulant therapy and ran a far less satisfactory course than the treated patients. From this preliminary clinical exploration, anticoagulant therapy may be regarded as a promising therapy in cases of cerebral thrombosis encountered in the earlier stages; certainly in our experience it seems more beneficial than any other mode of therapy used at present and it is relatively safe. The increasing frequency with which stroke patients are seen in the clinic, at a point in their illness when anticoagulants might be effective, indicates that this therapy may be of great significance in medical practice. The present data do not provide incontrovertible evidence of the therapeutic efficacy of anticoagulants because satisfactory control patients have not been studied.

The tentative indications for anticoagulant therapy in transient cerebral ischemic attacks and cerebral thrombosis have been discussed at some length.

The clinical picture of transient ischemic attacks has been described and their differential diagnosis discussed.

ILLUSTRATIVE CASE HISTORIES

Case 1. Group 1. Treated with anticoagulants. A 49 year old man. One hundred to 200 attacks of dizziness, diplopia, and weakness in five months. Almost no attacks while on Dicumoral for ten months. On stopping anticoagulant, attacks recurred but ceased on re-instituting therapy.

Five years before admission the patient began to have nocturnal seizures with tongue-biting, incontinence, and so on. These stopped one year before admission and the patient was symptom-free for seven months. Five months before admission he began to have repeated attacks of paralysis of one or other side of the body. They usually occurred about ten times each week, but sometimes there were three attacks in one day. Seven of each ten attacks affected the left side, three the right side. The attacks were clearly becoming worse. They were described as follows: First, a little dizziness was noted; then in 50 per cent of the attacks horizontal diplopia appeared. He felt weak and had to sit or lie down. One or other side became completely paralyzed but the other side was also weak. The patient was unable to speak, swallow, or turn over. He mumbled and drooled. He was fully conscious and could see, hear, and move the eyes. Later he was able to recall conversation heard during the attack. The attacks lasted five to 30 minutes, then recovery ensued in five to ten minutes. All had come on while sitting or standing. There was no complaint of headache, numbness, or twitching.

Examination on admission showed mild weakness of both hands, greater on the left. The tendon reflexes were brisk, the jaw jerk 4 plus, and a Babinski sign was noted bilaterally. Speech was slightly slurred and there was a mild finger-nose ataxia on the left. A diagnosis of basilar artery occlusion was made. The patient was given bed rest for one week and had no attacks. After a small dose of hexamethonium, the patient was tilted to an angle of 60° on a tilt table. The systolic blood pressure fell from 145/96 to 84 systolic without ill effect. Two hours later the patient, while sitting up in bed, greeted his wife and began to cry. Immediately he developed a transient right-sided paralysis. Four days later he had diplopia, dizziness, and weakness on sitting up in the morning.

The patient was placed on long term anticoagulant therapy and for ten months had no attacks, except on one occasion when, while hard at work, he had in succession three attacks of dizziness and weakness lasting about two minutes. Anticoagulants were gradually stopped after ten months, and within two months transient episodes began to recur, whereupon therapy was restarted with complete subsidence of the attacks in the ensuing eight months.

Case 2. Group 1. No anticoagulant, poor result. A 31 year old woman. Recurrent, transient episodes of hemiplegia, not relieved by papaverine, phenobarbital, or nicotinic acid, and terminating in a persisting hemiplegia.

The patient, a severely hyptertensive young woman, had at least ten attacks of temporary paralysis over a period of four months (February to June 1952). All attacks were similar and lasted only a minute or so. They were associated with a peculiar feeling in the head and epigastrium, the left hand became weak, and speech was slurred. There was no headache, numbness, or jerking. Neurologic examination between attacks was within normal limits and the patient felt well. The blood pressure was 220/130. Papaverine, 0.2 gm., and phenobarbital, 30 mg., three times a day did not alter the attacks and medication was changed to nicotinic acid, 50 mg., three times a day. While on this drug, the patient developed a complete left hemiplegia one morning while at work. This was associated with a headache above the right eye. Recovery was only fair, and the hand remained 50 per cent paralyzed. Anticoagulant therapy was recommended after the third attack but, because of the presence of severe hypertension, anticoagulants were not used.

Case 3. Group 1. No Anticoagulant, good result. A 56 year old man. Attacks of numbness for three months; cessation after stopping smoking; no recurrence in five years.

This patient had repeated attacks of numbness of the left hand and left cheek for three months. The first attack was the longest and most severe, lasting about ten minutes, and the function of the hand was mildly impaired thereafter. Approximately every four days he continued to have attacks of numbness lasting one to two minutes. Each attack started with a pins-and-needles feeling in the left cheek. There was also a feeling of movement, but his wife had examined his face during attacks and no movement could be seen. At almost the same time as the numbness appeared in the cheek, the left hand became numb. This feeling was deep in the hand and apparently involved the middle and ring fingers. Headache, visual disturbance, or weakness had never occurred. On neurologic examination the tendon reflexes were a little more active on the left and there was a left facial weakness.

The patient was placed on nicotinic acid therapy and also advised to stop smoking. The attacks gradually ceased over a period of five months, and five and a half years later the patient was well and working regulary.

Case 4. Group 2. Treated with anticoagulants, good result. A 70 year old woman. Basilar artery occlusion; repeated transient attacks associated with a gradually increasing neurologic deficit; anticoagulant therapy prevented attacks, which recurred on two occasions when therapy was interrupted. (This case was published in detail in Neurology 3:468, 1953). Anticoagulant was administered for six months (May to November

1952), and the patient was then well for four years until her death from myocardial infarction.

The patient was admitted to the hospital because of repeated transient episodes occurring once or twice a day for a month and described as follows: All power seemed to go out of her body; the right hand and occasionally the right face became numb and, in addition, there was a peculiar "terrible" sensation in her head. The attacks lasted only a few minutes, but usually an hour passed before she felt herself again. In addition, during the previous three weeks there had been three attacks in which the right wrist flexed forcibly and the hand became tight and drawn up. At the same time numbness appeared around the mouth. Closer questioning revealed there had been several further related episodes. Six months before, a sudden blackness swept before her eyes, she felt weak, and could not speak properly on the telephone. Four months before, while shopping, numbness or stiffness appeared around the mouth and she vomited precipitously over the counter of the store. She became ashen and felt confused for 10 to 20 minutes. Three months before, she had a five-minute attack of numbness of the entire right side of the body. Two months before, two attacks of dizziness and vomiting occurred, along with the sensation that a wire was being drawn tightly around her head. In between attacks she was quite well and neurologic examination a few days before admission was not remarkable.

During the first 18 days in the hospital she received Roniacol in doses of 50 mg. three times a day; there occurred many transient attacks of numbness and weakness of the right hand and right side of the face, slurred speech, weakness of the right leg, and difficulty in swallowing. Finally, recovery from these attacks was no longer complete, the right side remained weak, and a Babinski sign appeared bilaterally. A tentative diagnosis of basilar artery thrombosis was made and, since the picture was a progressive one, heparin and Danilone were begun in an attempt to forestall further thrombosis. Therapy was maintained for 33 days and there was no single episode of worsening during this time, although mild right-sided weakness still persisted. At this time anticoagulant therapy was stopped, and five days later there were three further brief attacks of numbness of the right hand and right side of the face, with blurring of vision. Fearing that a full-blown stroke was imminent, anticoagulant therapy was begun again in order to give time for a decision as to further management. For another 15 days Danilone was given and there were no transient episodes of any kind. Since the patient lived in a small village where facilities for the determination of the prothrombin time were not available, it was decided to try her once more without anticoagulants. Because of her dread of the attacks, a placebo pill almost identical with Danilone was given instead. Three days later when the prothrombin time had fallen to normal, the patient had two transient attacks of generalized weakness, slurred speech, and numbness of the right side. Two days later two more attacks occurred, in the second of which speech became slurred, swallowing was difficult, she could not see clearly, and the right side was numb. There seemed little doubt that anticoagulants had some beneficial effect and therapy was again started. Only three doses of heparin were given at four-hour intervals, instead of the usual six or more. Two days later, at a time when the Danilone had not yet become effective, the patient had an attack in which she became paralyzed in all limbs and was unable to speak, swallow, or see for about four hours. Heparin was given as an emergency measure and Danilone was continued. There were no further episodes and within a few days the patient was able to be up and around again. Therapy was continued for six months, during which time there were no untoward events.

The patient lived another four years and during that time there was no further neurologic disturbance, except for an episode of dysphagia lasting three days. The patient died from myocardial infarction. At autopsy the lower basilar artery was completely occluded by white connective tissue and an old softening was found in the lower basis pontis on the left side. To find complete occlusion of the basilar artery in association with a relatively asymptomatic clinical course over a period of years is a great rarity, and it would be reasonable to conclude that the use of anticoagulant drugs had allowed the patient to survive a crucial period in her illness, following which collateral blood flow was adequate to maintain the circulation in the territory of the blocked vessel.

Case 5. Group 2. No anticoagulant, poor result. A 54 year old man. Many transient attacks of numbness of the right face and hand, dysphasia, monocular amblyopia, and headache for three weeks. Two days after discharge from hospital, development of a severe right hemiplegia and aphasia. Occlusion of the internal carotid artery at autopsy.

This patient first attended the clinic complaining of attacks of numbness and loss of power in the right hand and numbness and a swollen feeling of the right side of the face. The attacks had begun one week before, coming twice the first day and three times the second day. They came day or night and lasted about two minutes. For eight or nine days he had had a frontal headache. Three days before, he had had blurred vision in the left eye. Neurologic examination was not remarkable. The blood pressure was 155/88. The patient returned one week later to say that he was now having the same type of attack five or six times each day. A more exact description of each episode included a moderate bilateral headache, numbness of the right side of the face, tongue,

and the right hand and wrist, some difficulty in speech, and colors in circular pattern before the left eye. The numbness of the face was as if it were "frozen" with a local anesthetic. All laboratory tests were normal. The patient returned a week later with a definite nominal dysphasia. He was admitted to the hospital for investigation and the cerebrospinal fluid, a pneumoencephalogram, and a ventriculogram were all normal. The dysphasia cleared gradually and the patient was discharged feeling very well. Two days later he awakened in the morning with a complete right hemiplegia and aphasia, from which recovery was extremely poor. The patient died four years later. At autopsy, the left internal carotid artery was found to be the site of an ancient occlusion.

Case 6. Group 3. Treated with anticoagulants, good result initially. A 55 year old man. Progressive downhill course with attacks of numbness, dizziness, and visual disturbance. On long term anticoagulant therapy, the transient ischemic attacks ceased and the patient noted no advance in his illness. Episodes recurred on stopping anticoagulants after 18 months, but on resuming therapy they subsided once more. After another year on anticoagulants, progressive gradual paralysis and death from basilar artery occlusion ensued.

In August 1951 the patient began to have attacks of numbness of the right hand and foot lasting one to two minutes and occurring three or four times a month. Vision was poor in the right visual field and the patient had sideswiped a passing car. In November 1951 he complained of a dull frontal headache and persistent numbness of the right face, arm, and leg; a right homonymous hemianopia was found. In April 1952 there occurred a prolonged episode characterized by dizziness, nausea, vomiting, deafness of the right ear, tinnitus, and ataxia of the right arm and leg. Recovery was incomplete. Dizzy spells continued (three to four each week) and in May 1953 the patient suddenly became disoriented for 15 minutes. In June 1953 he began to have attacks marked by sudden numbness of both hands, blindness, and severe right frontal headache. Finally, poor vision persisted and the patient's memory was noted to be poor. Dicumarol therapy was started in July 1953 and maintained for 18 months with no further episodes. (A serious neurologic residuum persisted, however). At the end of this period anticoagulants were discontinued and for four months the course was uneventful. Then there appeared in sequence occipital headache, attacks of dysarthria, numbness of the right side, and episodes of complete inability to move. After two months of observation on nicotinic acid therapy (50 mg. three times a day), the patient was having attacks almost every day; he was virtually blind and unable to feed himself or walk unaided. Heparin and Dicumarol were started again and within seven days he was much improved. In the ensuing year he had no further attacks while anticoagulants were continued. Despite adequate anicoagulants, symptoms recurred after two and three-quarter years on therapy, and over a period of three weeks the patient became more confused, weaker and more ataxic; gradually paralysis of all four limbs ensued. Stupor and coma appeared and the patient died. Pathologic examination showed virtually complete occlusion of the basilar artery by atherosclerosis and recent thrombus was absent. The blockage lay near the upper end of the artery. Both posterior cerebral arteries were the site of old occlusion.

The attempt to withdraw anticoagulants a year before death with marked worsening of the patient's condition, followed by the remission of symptoms when therapy was re-instituted, is almost certain evidence that anticoagulants had a favorable effect. The ultimate failure of the anticoagulant therapy is well illustrated.

Case 7. Group 3. No anticoagulant, attacks continued. A 64 year old man. Bout of severe vertigo with persistent nystagmus. Blood pressure 240/120. Anticoagulant therapy deferred because of hypertension. Observed for two years, transient attacks occurring off and on without resulting in a stroke. Nicotinic acid therapy.

This patient first noticed mild attacks of dizziness five days before admission, along with a slight "puff" sound deep in the left ear. On the day of admission, whirling dizziness became violent and he was unable to stand or sit up. On admission the only neurologic abnormality was horizontal nystagmus, greater on gaze to the left. Audiograms and caloric tests were normal. The blood pressure was 240/120. Recovery from dizziness was extremely slow and nystagmus persisted. A tentative diagnosis of vertebral artery disease was made. Nicotinic acid (50 mg. three times a day) was prescribed, and during the following months he reported the following: six months after discharge, five transient attacks of diplopia combined with numbness of the left leg; seven months after discharge, blurred vision and weakness of both legs; 12 months, "several" attacks of blurred vision; 17 months, an attack of confusion, blurred vision, weakness and numbness of the right leg, slurred speech, the entire episode lasting ten minutes; 19 months, diplopia four or five times, two attacks in which one leg became weak, the right on one occasion, later the left; 24 months, one attack of slurred speech for ten minutes, five or six attacks of numbness of the left side of the face each day for one week. Although attacks have continued, no permanent damage to the nervous system has resulted.

Case 8. Group 4. Treated with anticoagulants, good result. A 69 year old woman. Progressive neurologic deficit for two weeks, arrested by heparin and Dicumarol.

This patient had had an excruciating, pounding, bifrontal headache for seven days. It interfered

with sleep and medication gave no relief. The whole head was filled with an intolerable gushing, throbbing sound like a "huge river running." Two days after the disappearance of the headache, while using her treadle sewing machine, the right foot and leg became weak for half an hour but immediately afterward the patient walked normally. The next day on awakening in the morning, the right leg was weak and walking was difficult. Eight years before, a radical mastectomy had been performed for carcinoma.

On admission to the hospital, the only abnormalities were an unsteady, shuffling gait and mild weakness of the right lower extremity. The blood pressure was 130/100. During the first week in the hospital the right leg became weak. Next, the right arm showed increasing weakness and, finally, the left leg. The patient had become bedridden and unable to turn over. Secondary carcinoma of the brain was suspected, but discrepant findings were lack of pulsation of the left internal carotid artery and the presence of a systolic bruit over the eyeball on the right side. A diagnosis of occlusive vascular disease of the left internal carotid artery was made and heparin and Dicumarol were started. The downward course of the illness was arrested and by the next day mild improvement was evident. Recovery was satisfactory except for persistent paralysis of the right leg.

Case 9. Group 4. Treated with anticoagulants, good result. A 67 year old woman. During the month before admission the patient had noted attacks of confusion, vertigo, nausea, vomiting, ptosis, deafness, tinnitus, diplopia, and weakness of the right arm. After admission to hospital, right hemiplegia occurred. Anticoagulant therapy was begun, and, despite further transient worsenings, extremely good recovery occurred.

One month before admission to the hospital this patient had an episode at the dinner table one evening in which she spoke in an absent-minded manner, repeating rather simple ideas over and over. Someone had presented a piano to the parish and the patient would say, "Isn't it wonderful we have a new piano . . . . we should be proud to have a new piano . . . . it certainly means everyone is doing his part for us to get a piano . . . ." and so on. Five minutes later she had returned to normal. In the following two weeks two similar episodes occurred. Two weeks before admission spinning dizziness was first noted, coming in daily attacks and causing her to vomit. At times there was ringing of the ears. The dizziness became worse, prostrating her with nausea and vomiting. Four days before admission deafness of the right ear was noted. Two days before admission she collapsed over a bed; on regaining consciousness, the right hand was numb and useless and she thought she had been lying on it. The hand recovered function in the next 24 hours. On the same day there was another episode of confusion and the patient noted diplopia, particularly on gaze to the left. The dizziness was aggravated by movement and on trying to sit up; the eyes would dart to the right side and could not be controlled.

Examination on admission showed the patient was incapacitated by dizziness and vomiting. There was nystagmus on lateral and vertical gaze. Ptosis was present on the left. There was bilateral crossed diplopia with diagonal displacement of the images. Motor and sensory functions of the limbs were normal. The blood pressure was 150/90.

The day after admission at 8:15 p.m. the patient developed a right hemiparesis involving face, arm, and leg. At the onset the arm and leg were totally immobile. Dizziness, deafness, tinnitus, and diplopia continued.

Dicumarol was begun and in 48 hours the prothrombin activity was less than 10 per cent. Power in the right leg was much better but the hand was still very weak. Four days after beginning Dicumarol the patient had two attacks of pins-and-needles numbness of the left arm and leg and two separate attacks of numbness of the left side of the face lasting three to five minutes. Her course was one of improvement for the next five days, but on the tenth day after starting Dicumarol there was a one-hour attack of numbness of the left side of the body and a transient complete paralysis of the right side of the face. Long term Dicumarol was continued and recovery was uneventful. Paralysis, diplopia, dizziness, and ptosis gradually cleared; three months later there were no definite abnormalities, except partial deafness in the right ear.

This is an example of a progressive illness which appeared to be reversed by the anticoagulant, although temporary worsenings occurred for several days after anticoagulant therapy was begun.

Case 10. Group 4. No anticoagulant, poor result. A 68 year old woman. Stuttering or stepwise development of aphasia and right hemiplegia over a period of several weeks. Anticoagulant therapy suggested, but not administered until later. Severe persistent deficit, finally fatal.

While in the hospital for investigation of a gastrointestinal complaint, this patient had a brief episode (a few minutes) of anarthria early one morning after an enema. Fifteen minutes after speech had returned, speechlessness recurred and persisted. There was severe weakness of the right lower face. Anticoagulant treatment was recommended on the premise that the deficit might represent only part of a threatening larger stroke, but a conservative course was pursued. Three weeks later receptive aphasia, which came in a step-wise fashion, was added to the picture, along with weakness of the right hand and ideational apraxia. Anticoagulant therapy was then begun and maintained for approximately eight weeks. Recovery was poor and anticoagulant therapy was stopped. Within a month, further paralysis of the right side occurred and death followed. (No autopsy).

Case 11. Group 4. No anticoagulant, poor result. A 58 year old man. For four months the patient had dizziness, impaired hearing, and tinnitus. Later occipital headache and attacks of confusion appeared. Investigation in hospital was not remarkable. Shortly after discharge, development of progressive quadriplegia and coma. Vertebral artery occlusion at autopsy.

The patient, a known hypertensive (180/120), began to have episodes of dizziness with impaired hearing and tinnitus in the left ear four months before admission. For one month there was occipital headache off and on. One week prior to entry he began to have episodes of memory loss lasting only a few minutes at first, later half an hour. He was a salesman and on the day after a holiday, thinking it was Monday, he called on his Monday customers by mistake. Apparently he talked clearly during the episodes. During the entire day before admission he had blurred vision. Examination on admission was not remarkable. On the third hospital day he became confused for a few minutes, remembered nothing, and wanted to know why he was in hospital. There was associated excitement and he had to be restrained. On four successive days he had similar episodes lasting about 15 minutes. Between attacks he was perfectly alert and oriented. He was discharged without anticoagulant therapy, and the following evening weakness of the legs and slurred speech were noted. Over the next four days he became increasingly incapacitated with quadriplegia, dysphagia, dysphonia, and vertical and horizontal nystagmus, and he died in one week. Pathologic study showed a recent vertebral-basilar artery occlusion with brainstem infarction.

REFERENCES

1. Fisher, M., and Cameron, D. G.: Concerning cerebral vasospasm. Neurology 3:468, 1953.
2. Hedenius, P.: The use of heparin in internal diseases. Acta med. scandinav. 107:170, 1941.
3. Denber, C. B.: Thrombose cérébrale et héparine. Schweiz. med. Wchnschr. 75:192, 1945.
4. Rose, W. McI.: Anticoagulants in the management of cerebral infarction: A record of the poor results obtained. M. J. Australia 1:503, 1950.
5. Fisher, M.: Occlusion of the internal carotid artery. Arch. Neurol. & Psychiat. 65:346, 1951.
6. Wright, I. S., and Luckey, E. H.: Transactions of the Conference on Cerebral Vascular Diseases, January 1954. Grune & Stratton, New York, 1955, p. 94.
7. Campbell, M. H.: Basilar artery syndrome. Canad. M.A.J. 69:314, 1953.
8. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebrovascular disease. III. The use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. Proc. Staff Meet., Mayo Clin. 30:116, 1955.
9. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebrovascular disease. V. The use of anticoagulant drugs in the treatment of intermittent insufficiency of the internal carotid arterial system. Proc. Staff Meet., Mayo Clin. 30:578, 1955.
10. Wright, I. S., and McDevitt, E.: Cerebral vascular diseases: Their significance, diagnosis and present treatment including the selective use of anticoagulant substances. Ann. Int. Med. 41:682, 1954.

■ Physiologists, both ancient and modern, have very generally considered the *immediate*, or *proximate* cause of apoplexy to be an obstruction of the passage of the nervous fluid into the organs of sense and motion. This was the opinion of Galen and his disciples. Apoplexy and epilepsy, he says, seem to be generated by a quantity of pituitous humour collected in the ventricles of the brain, which obstructs the passage of the animal spirits from the ventricles: and again, apoplexy, by the suddenness of its attack, denotes a cold, or thick, or viscid humour entirely filling the principal cavities of the brain.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

The electroencephalogram in metastatic tumors of the brain

Donald W. Klass, M.D.* and Reginald G. Bickford, M.B.

SINCE Grey Walter demonstrated in 1936 that the electroencephalogram can be used to localize cortical tumors,[1] many reports have appeared confirming this early impression on the basis of much more extensive material. Most authors have dealt primarily with the findings in primary tumors of the brain.[2-6] This paper will review the electroencephalographic findings in a series of cases of metastatic tumors of the brain to determine the accuracy of the electroencephalogram in localization of these lesions, and to ascertain whether or not the characteristics of the recordings differ from those obtained in the presence of primary tumors.

The incidence of metastatic tumors of the brain secondary to malignant processes situated elsewhere in the body, as given in published reports, varies from 2.15 to 35 per cent.[7,8] Metastatic lesions constitute about 17 per cent of all tumors of the brain.[9] The importance of these lesions, however, lies not only in the fact that they account for so many brain tumors, but also in the fact that the prognosis for patients thus afflicted is very poor.[10] Moreover, these lesions are important to the neurologist and neurosurgeon, because they frequently present clinical problems in diagnosis when the primary malignant process situated elsewhere has not been found. Even if the site of the primary lesion is known, there remains the problem of deciding whether or not neurosurgery should be done, either for palliation or for attempted cure, since "benign" intracranial lesions have been known to occur in patients with proved extracranial malignant lesions.

MATERIAL

The records of all patients with the final clinical diagnosis of tumor of the brain from whom an electroencephalographic recording had been obtained between January 1, 1952 and June 30, 1954 were extracted from the files of the electroencephalography laboratory of the Mayo Clinic. There were 456. In 42 of these, or 9.2 per cent, the lesions had been diagnosed as metastatic. The histories, electroencephalographic records, and surgical and pathologic data were reviewed. It can be assumed that most patients suspected of having an intracranial lesion are referred for electroencephalographic studies at this clinic, especially if craniotomy is contemplated. In a few instances, however, an electroencephalogram is not made, such as when an emergency operation is necessary or when the patient is in poor general condition or when the clinical diagnosis is not at first suspected. Otherwise, the total group is selected only in the matter of the type of patient seeking care at a large private clinical institution.

PATHOLOGIC ASPECTS

Of the 42 lesions diagnosed clinically as metastatic tumors of the brain, 32 were confirmed by pathologic examination, either at the time of operation or at necropsy. Ten were diagnosed presumptively on the basis of clinical and laboratory findings alone. The ages of the patients ranged from 22 to 76 years. There were 16 women and 26 men. The incidence according to age is given in table 1.

The greatest incidence, occurring in the fifth and sixth decades, is in agreement with the data obtained at postmortem studies by Kiefer[11] and by Lesse and Netsky.[7] The latter

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TABLE 1
INCIDENCE ACCORDING TO AGE

Range, years	*Patients*
10 to 19	0
20 to 29	1
30 to 39	5
40 to 49	12
50 to 59	15
60 to 69	8
70 to 79	1

found in their series that the tumors metastasizing to the nervous system developed earlier during the life of the patients than do the majority of primary neoplasms, of which the greatest incidence is in the sixth and seventh decades.

Prior to initial examination of the patients at this clinic, symptoms suggesting intracranial involvement had been present for an average of only two or three months. Seizures of all types had taken place in 21 per cent, a figure lower than that for the seizures which accompany most malignant primary tumors of the brain.[12] The great majority of tumors were adenocarcinomas. The tumors were graded on the basis of increasing malignancy, 1 to 4,[13] in 28 cases. Of these, none was grade 1, eight were grade 2, seven were grade 3, and 13 were grade 4. The foregoing clinical and pathologic data serve to show that the lesions generally were of a relatively high degree of malignancy. The site of the primary tumor was found or had been known in 31 of the 42 cases. In the remaining 11 cases a thorough search for an occult primary location was unsuccessful or was deemed inadvisable because of the patient's condition or after discussion with the family. By far the most frequent primary site was the lung (17 cases). Whether one or more intracranial lesions were present could be determined accurately only by necropsy. The group of cases in which postmortem examination was done was small (nine cases). In this group lesions were single in five cases and multiple in four. In a larger series of postmortem examinations, Kiefer[11] found that 30 per cent of metastatic lesions to the brain were single and that 70 per cent were multiple.

SYMPTOMS

The initial symptoms of intracranial involvement most frequently were nonlocalizing and consisted of headache, with or without change in mental status of affect, memory, or personality. One person had received electroshock treatment before arrival at this clinic, because of personality change. At necropsy in this instance, internal hydrocephalus secondary to a solitary metastatic lesion in the right cerebellar hemisphere was found. The onset of neurologic symptoms was marked by seizures in only five cases. The most frequent findings during the initial neurologic examination were a motor weakness or ataxia and incoordination. In only 13 cases was optic papilledema detected. In every case a tumor of the brain was suspected on clinical grounds, and this undoubtedly was a factor in selection of cases for this series. In 13 cases the metastatic nature of the lesion was not suspected, and in none of these was the primary lesion evident before craniotomy was performed.

RECORDING TECHNIC

Fourteen electrodes (five in the parasagittal rows, one in the sylvian area, and one to each ear) were applied routinely, and care was taken to control artifacts caused by movements of the eyes. All recordings were carried out with an eight-channel Grass instrument. Recording time was 45 minutes, which included a three-minute period of overbreathing and photic stimulation at flash frequencies ranging from one to 30 flashes per second. Bipolar and monopolar recordings were made on each patient, localizations being based on data from bipolar recordings, which are found to be much more reliable in this respect, due to cancellation of diffuse rhythms and the increased visual sensitivity associated with a two-channel, out-of-phase display. The criteria of abnormality adopted were those in use in this laboratory.[14]

RESULTS

For the group as a whole, it was found that two patients (5 per cent) had normal electroencephalographic patterns and 40 patients (95 per cent) had patterns showing some degree of abnormality, either focal or generalized. The two patients who had normal

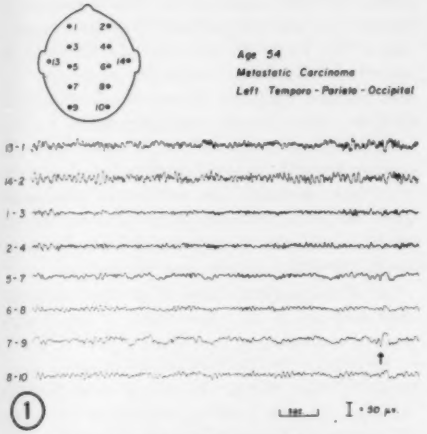

FIG. 1. Electroencephalographic tracing showing intermingled focal slow-and-sharp abnormality in an instance of metastatic tumor.

patterns were found to have lesions situated near the base of the brain, one in the left frontal region and the other in the posterior fossa. In 29 cases there was evidence of focal abnormality, usually in the form of localized waves of ½ to 3 cycles per second. In 12 of these cases there were scattered slow discharges characterized by rather sharp contours, interspersed among the more irregular delta waves (figure 1). Seven contained a bilateral abnormality of the "projected type," as described by Daly and associates,[15] suggesting a deep midline lesion or a lesion of the posterior fossa. Four records contained a bilateral or generalized abnormality which was nonlocalizing.

Although separate delta foci with phase reversal are known to occur in the presence of multiple lesions, there were no examples of this in the group under consideration. When multiple lesions were known to be present on the basis of necropsy data, the tracings were reviewed, but the abnormalities, instead of forming separate foci, seemed to merge and produce a more widespread disturbance in either one or both hemispheres.

The alpha rhythm frequently was disorganized in the presence of a hemispheric lesion, being diminished on the side of the lesion in half such cases. The driving response produced by intermittent photic stimulation also was frequently disorganized on the side of the lesion. In no case was this response increased over that of the affected hemisphere, in contrast to the alpha rhythm, which was of higher voltage on the side of the lesion in four of 22 cases. Only one record of the entire 42 was characterized by prominent fast activity.

The effects of opening the eyes, mental activity, and hyperventilation on the electroencephalogram also were tabulated. Minimal inhibition of the abnormalities, regardless of frequency, was noted during opening of the eyes and mental activity in the form of calculation. However, a decisive inhibition predominantly accompanied discharges of 4 to 7 cycles per second and only rarely accompanied the focal slower waves. Hyperventilation for a period of three minutes had only a minimal effect on the abnormalities.

The accuracy of the electroencephalogram could be judged only in 32 cases in which a lesion was confirmed by operation or necropsy. In 26 (81 per cent) the electroencephalogram could be considered as localizing to some extent. In 17 cases (53 per cent) the electroencephalogram localized the correct side and lobe, and in an additional three (9 per cent) it established the correct side alone. In six cases (19 per cent) it localized the lesion to the deep midline or posterior fossa regions. In three cases the patterns were abnormal but were reported as nonlocalizing, and all three of the patients concerned had lesions in the deep midline or posterior fossa regions. Two patterns were normal, as described previously. One addtional case must be held open for consideration, since it is the only case in which the electroencephalogram might have localized the lesion incorrectly. In this instance there was a definite left temporal delta focus, but ventriculograms showed symmetric dilatation of the lateral ventricles. At operation the posterior fossa was explored and a cerebellar lesion was found. This patient was still alive at the last report, but it is not possible to state whether he has an additional lesion in the left temporal region, as the electroencephalogram would suggest.

COMMENT

The electroencephalogram has been established as having unquestioned value as an aid

in the localization of tumors of the brain. Yeager and associates[6] in 1940 reported that in 86 per cent of 43 hemispheric tumors the electroencephalogram provided accurate localization, whereas localization was not obtained in 9.3 per cent, and in 4.7 per cent of cases the localization provided by the pattern was doubtful. Kershman and co-workers[5] found that in 100 cases of supratentorial tumors correct localization was provided by the electroencephalogram in 77 per cent, in 20 per cent localization was poor, and in 3 per cent localization to the wrong side was noted.

Accuracy of localization depends on the location of the tumor, as shown by the study of Amador,[2] in which the accuracy of the electroencephalogram in localizing cortical tumors was 84 per cent, while in localization of cerebellar tumors the accuracy of the electroencephalogram was 60 per cent. It was only 29 per cent when deep-seated lesions were present. In the 543 cases of verified tumor reported by Hoefer and associates[16] there were 37 metastatic lesions. The accuracy of the electroencephalogram was reported only in respect to localization of hemispheric lesions. Of the 30 hemispheric tumors, 20 were localized by the electroencephalogram, three were lateralized, five were not localized by this means, and two were localized falsely. In their total series the authors found that the electroencephalogram had provided false hemispheric localization in eight of 41 midline and in 17 of 86 tumors of the posterior fossa.

In our series of 32 verified metastatic intracranial lesions, regardless of location, the electroencephalogram localized the lesions to the correct side in 81 per cent. There were two normal patterns (6 per cent), and both of the patients concerned had lesions situated near the base of the brain. In a recent report on a small (100), unselected group of tumors of the brain from our laboratory, it was indicated that the electroencephalogram will provide correct localizing or lateralizing information in 86 per cent of cases.[17] This figure agrees with the results of the present study of electroencephalographic localization of metastatic tumors.

A different method of approach to show the value of the electroencephalogram in metastatic lesions was used by Gastaut and co-workers.[18] He studied the electroencephalograms of a series of patients who had carcinoma of the lung. In his study, in all instances in which it had been clinically suspected that the patient had an intracerebral metastatic process, the electroencephalographic pattern was confirmatory. In 12 of 24 cases in which it had been thought clinically that metastasis was not present, the electroencephalogram gave evidence of hemispheric lesions. In ten of 12 cases with no metastasis, the electroencephalographic pattern was normal.

It would appear, then, that the electroencephalogram is of value both in confirming and in excluding a metastatic cerebral lesion.

In respect to the factors of range of ages, primary sites, initial symptoms, and physical findings, there is good agreement in our series of cases with the same factors reflected in the data reported by others.[7,11] Since the initial symptoms most often are nonlocalizing, electroencephalographic tracings made at the time of appearance of those symptoms may be of value in an attempt to obtain earlier diagnosis and localization.

The gross appearance of a metastatic lesion of the brain, although such a lesion may be highly malignant, is variable, but the tumor often is sharply demarcated from the surrounding portions of brain, which in turn show evidence of degeneration. It might be supposed that this picture could account for the rather frequent appearance of sharp or spiky discharges in the electroencephalogram, such as are generally associated with atrophic, degenerative, or slowly progressive lesions. However, in our study we found no correlation between the presence of such discharges and the gross appearance of the tumor, the presence of seizures, or the grade of malignancy of the tumor.

In 12 cases in our series sharp or spiky discharges were recorded. Three of the patients concerned had had seizures. Among nine other patients in this series with a history of seizures, three had electroencephalographic evidence of sharp discharges. Although it is somewhat surprising to see the rather frequent appearance of such discharges in the presence of such malignant lesions, these waves certainly cannot be considered diagnostically specific, even for this type of tumor.

Kershman and associates[5] recorded "focal sharp" discharges in the presence of primary tumors of the brain; most frequently these discharges were associated with astrocytomas. In fact, no criterion thus far has been found with which to distinguish a metastatic from a primary tumor of the brain by the agency of the electroencephalogram. Greenstein and Strauss[19] found that a high percentage of metastatic tumors of the brain have a "focal per cent time delta" greater than 40, but this also occurred in a similar percentage of tumors of the brain of the more malignant type.

CONCLUSIONS

1. The electroencephalogram provides a high degree of accuracy in the localization of metastatic tumors of the brain, an accuracy comparable to that obtained in the electroencephalographic localization of primary tumors of the brain.

2. In cases of suspected metastatic tumor of the brain, a normal electroencephalographic pattern can be of considerable help in excluding an intracranial lesion.

3. Frequently it is not possible to determine with certainty by means of the electroencephalogram whether or not multiple lesions are present.

4. There is no pathognomonic electroencephalographic picture which differentiates primary and metastatic tumors of the brain.

5. The possibility of a metastatic lesion should be considered when a middle-aged person reports the recent gradual onset of intracranial symptoms and when a focal abnormal electroencephalographic pattern is obtained from such a person.

REFERENCES

1. Walter, W. G.: The location of cerebral tumours by electroencephalography. Lancet 2:305, 1936.
2. Amador, L. D.: Accuracy of preoperative electroencephalographic localization in neurosurgery. Arch. Neurol. & Psychiat. 65:407, 1951.
3. Cuneo, H. M., Rand, C. W., and Sjaardema, H.: Analysis of electroencephalographic findings of 40 cases of verified brain tumor: Electroencephalographic findings in metastatic tumors of brain. Bull. Los Angeles Neurol. Soc. 14:149, 1949.
4. Case, T. J., and Bucy, P. C.: Localization of cerebral lesions by electroencephalography. J. Neurophysiol. 1:245, 1938.
5. Kershman, J., Conde, A., and Gibson, W. C.: Electroencephalography in differential diagnosis of supratentorial tumors. Arch. Neurol. & Psychiat. 62:255, 1949.
6. Yeager, C. L., Baldes, E. J., Craig, W. McK., and Woltman, H. W.: Electroencephalography as an aid in localizing intracranial lesion. Proc. Staff Meet., Mayo Clin. 15:147, 1940.
7. Lesse, S., and Netsky, M. G.: Metastasis of neoplasms to central nervous system and meninges. Arch. Neurol. & Psychiat. 72:133, 1954.
8. Neustaedter, M.: Incidence of metastases to nervous system. Arch. Neurol. & Psychiat. 51:423, 1944.
9. Baker, A. B.: Metastatic tumors of the nervous system. Arch. Path. 34:495, 1942.
10. Rupp, Charles: Metastatic tumors of the central nervous system. I. Intracerebral metastases as the only evidence of dissemination of visceral cancer. Arch. Neurol. & Psychiat. 59:635, 1948.
11. Kiefer, E. J.: Metastatic Brain Tumors. Thesis, Graduate School, University of Minnesota, 1947.
12. Daly, David, MacCarty, C. S., and Bickford, R. G.: Seizures in patients with gliomas of the cerebral hemispheres. Tr. Am. Neurol. A. 75:159, 1950.
13. Kernohan, J. W., and Sayre, G. P.: Tumors of the Central Nervous System. In: Armed Forces Institute of Pathology. Atlas of Tumor Pathology, Section 10, Fascicles 35 and 37, pp. 1-129. Washington, D.C. National Research Council, 1952.
14. Sections of Neurology and Physiology, Mayo Clinic: Clinical Examinations in Neurology. Philadelphia, W. B. Saunders Co., 1956, 370 pp.
15. Daly, D., Whelan, J. L., Bickford, R. G., and MacCarty, C. S.: Electroencephalogram in cases of tumors of posterior fossa and third ventricle. EEG & Clin. Neurophysiol. 5:203, 1953.
16. Hoefer, P. F. A., Schlesinger, E. B., and Pennes, H. H.: Clinical and electroencephalographic findings in a large series of verified brain tumors. Tr. Am. Neurol. A. 71:32, 1946.
17. Bickford, R. G.: Electroencephalographic diagnosis of brain tumors. Am. J. Surg. 93:946, 1957.
18. Gastaut, H., Roger, A., and Chatrian, G. E.: Electroencephalographic findings in cases of lung cancer. EEG & Clin. Neurophysiol. 6:525, 1954.
19. Greenstein, L., and Strauss, H.: Correlation between electroencephalogram and histological structure of gliogenous and metastatic brain tumors. J. Mt. Sinai Hosp. 12:874, 1945.

What neurologists should know about international neurologic congresses

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THE MAIN OBJECTIVE of the First International Congress of Neurological Sciences (ICNS), held in Brussels July 21 to 28, 1957, was to return to the central orbit of neurology its related specialized disciplines which had begun to secede, each one organizing an international congress of its own. This objective, largely, was attained. By creating an operable synthesis of neurologic disciplines, the ICNS in Brussels did much to restore to neurology the central prestige it merits. The delegates of all the constituent congresses of the ICNS, except neurologic surgery, left Brussels with a sense that this kind of interdisciplinary rapport and cross-fertilization was essential to their future, even though the Brussels pattern could not be repeated for all future congresses.

In Brussels, too, it was evident that scattered international congresses held for each category of neurologic discipline entail, for those neurologists and neurologic scientists who wish to attend them all, large expenditures of time and money which may be reduced to a minimum if the congresses are combined and meet simultaneously.

PAST INTERNATIONAL NEUROLOGIC CONGRESSES

For almost 40 years international neurologic congresses† have been organized by a distinguished group of senior neurologists from a small number of countries who, through an exclusive program committee, planned the total program and divided among themselves the responsibilities for the conduct of these congresses. While their results were brilliant—no one criticizes or questions them—the ever-growing complexities and costs attached to the organization of international congresses, including the rising personal expenses for those who wish to attend them, call for a change in the basic orientation of such programs.

Further, since the preliminary meeting in 1947 of the executive program committee for the Fourth International Neurological Congress (Paris 1949), new trends for a change in the organization of international neurologic congresses were discernible. In general, these trends called for a change in the classic structure of the scientific programs of these congresses. More specifically, they encompassed two major objectives: 1) the creation of a greater freedom and range of interest in the selection of topics and topic directors‡ for the scientific sessions, which would reflect more realistically the prevailing sentiments of the national delegates who composed the executive committees of the congresses; and 2) a greater consideration to geographic and cultural factors in the selection of important participants for the scientific sessions.

†The first International Neurological Congress was held in Basel (1931), the second in London (1935), the third in Copenhagen (1939), the fourth in Paris (1949), and the fifth in Lisbon (1953).

‡In congress terminology, the topic directors are the chairmen of planned symposia or of sessions related to a central theme.

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Obviously, the development of these trends was associated with the growing dispersion of neurology and neurologic science to all parts of the world after World War II and the progressive enlargement of the scope of neurology resulting from the discovery of new methodologies and new technics. The impact of these innovations was not precipitous, but it was insidious and sure. At the Paris Congress in 1949, the traditional type of program still could be maintained and controlled to a certain extent by the senior group of neurologists. But by the time of the Lisbon Congress in 1953 (Fifth International Neurological Congress), so indisputable were the demands for a broader and representative freedom in the selection of topics and topic directors that a change seemed inevitable.

Of course, these developing trends introduced new problems calling for a reorientation in the planning and conduct of future congresses, namely: 1) an ever increasing number of free communications* submitted for inclusion in the scientific sessions; and 2) a growing dissension on the part of some congressionalists, who also belonged to specialized neurological disciplines (neurosurgery, neuropathology, electroencephalography, epilepsy, and so on) and were welding themselves into autonomous groups.

Since the Paris Congress the number of free communications submitted for the scientific sessions had increased to an alarming degree. Attempts to cope with the situation by increasing the number of sessions in a greater number of auditoriums resulted only in smaller audiences at these sessions, which discouraged many authors so that they appeared late or not at all to make their presentations. The increasing number of free communications also posed a problem of increased costs for the publication of transactions and for additional demonstration and projection equipment.

Also in Paris many of the investigators and clinicians representing specialized neurologic disciplines were still incorporated in the Fourth International Neurological Congress, but sufficient dissension was detected among them that, at the end of the Congress, a liaison committee was appointed to bind the interests of these groups more closely to those of neurology.

*Free communications refer to miscellaneous papers, initiated individually, and not submitted as part of a planned symposium or topic.

CRISIS IN LISBON

At the Fifth International Neurological Congress in Lisbon in 1953, these tendencies to dissension and secession became more pronounced, even though much of the program had been devoted to neurologic surgery. Although a rupture was not proclaimed openly, certain members of the Congress turned again to the liaison committee which had been appointed to ameliorate the situation. It was then quite evident that, for all practical purposes, this committee had no authority, except for a few points about which everyone agreed.

Briefly, the Lisbon Congress demonstrated: 1) a lack of cooperation on the part of some authors who presented their papers late or not at all because they considered their audiences too small and unworthy of them; 2) the crushing weight of the increasing number of free communications which evoked relatively little interest; 3) the failure of holding many small sessions devoted to free communications, as compared to the success of large symposia; and 4) the susceptibility of national pride when selection of authors was made, which hampered the freedom of a topic director to choose his own collaborators.

From the Lisbon Congress, it was obvious that, if these defects were not overcome, there would result in the future: 1) an accumulation of papers of slight interest but costly to publish, reflecting the numerical increase of the free communications; 2) a group of presentations by scientific personalities who had been selected because of complex national and cultural pressures rather than on the basis of their scientific competence; and 3) a reduction in the high academic level of neurologic programs, resulting in a decline in attendance at international neurologic congresses, which would be to the advantage of the growing "splinter" congresses of the specialized neurologic disciplines.

THE BRUSSELS PLAN AND ITS OPERATION

When the committee of national delegates in Lisbon had named Brussels as the site for the next neurologic congress, these exigencies were studied, and in 1955 the Belgian National

Committee proposed: 1) to reorganize all the specialized neurologic disciplines along the central axis of neurology by investing them in a coordinated program, which would allocate two days for major topics of common interest to all the constituent groups and two days for independent sessions of each participating discipline;* and 2) to reduce to a minimum the time allocated for free communications.

Such a compact program vitiated the free day usually set aside for excursions. Such a program also required the availability of many large and easily accessible auditoriums, either adjacent to one another or grouped together so that all participants in the congress, supplied with a map, could go quickly from one auditorium to another in pursuit of their special interests.

The selection of topics and topic directors for the Brussels Congress was made at the preliminary meeting of the program committee in 1955. The topic director, once selected, was given absolute jurisdiction in the choice of his collaborators and discussors and in the amount of time granted to each one. However, it was agreed that the directors of topics of common interest would contact the heads of each of the other constituent disciplines of the congress for contributions to the program.

For maximum coordination the secretariats of the neurologic and neuropathologic congresses were to be under the supervision of a single director and, similarly, the secretariats of the electroencephalography and epilepsy groups were under another director. The secretary-general chosen by the First Congress of Neurological Surgery was Professor M. David of Paris, assisted by Dr. William B. Scoville (Hartford, Connecticut, U.S.A.). The secretary-general of the neuroradiologic symposium was Professor J. G. Melot of Brussels.

All of these individual congresses were combined to form the First International Congress of Neurological Sciences, having as president, Professor P. van Gehuchten; secretary-general, Dr. Ludo van Bogaert; and assistant secretary-general, Dr. J. Radermecker.

Obviously, such a complex program required a concentration of administrative matters in the hands of a few persons having constant contact with each other. Accordingly, with the concurrence of Professor David, Dr. Brihaye (Brussels) was appointed to serve as local secretary of the Congress of Neurological Surgery, with an assistant, Dr. J. Soetens of Antwerp.

Even this system was still imperfect. If an administrative task of this magnitude, straddling two continents as it did, is to proceed without delay, it is essential to have an assistant secretary-general representing all of the constituent disciplines on one continent. He would have the responsibility of handling registrations, recording relevant facts, and transmitting them regularly to the office of the secretary-general of the combined congress on another continent. The same administrative principle applies for the office of the treasurer.

This mechanism functioned perfectly for the congresses of neurology, neuropathology, electroencephalography, and epilepsy, under the supervision of Dr. Pearce Bailey, who assumed the responsibilities of an assistant secretary-general for North America. It functioned less efficiently for the Congress of Neurological Surgery owing to the delays and uncertainties occasioned by routing through Paris information which was destined for Brussels.

The secretary-general (ICNS), in his efforts to evaluate the scientific potential of various countries to contribute to the principal topics of the program, forwarded to the various national committees of the constituent congresses an appeal to compose a roster of scientists who, as representatives of countries or of particular geographic regions, might be considered as promising candidates for the submission of formal papers or to serve as discussors. Two-thirds of the countries replied and their replies were forwarded to the appropriate topic directors for their information. In this way, the topic directors were given free rein in the selection of their collaborators and, at the same time, had complete information on potential participants at their disposal. The topic director also was responsible for the return of manuscripts of his collaborators and for communicating their contents to the various discussors. This arrangement placed the topic

*At Brussels two full days were devoted to the two major topics of common interest, "Extrapyramidal Pathology" and "States of Consciousness in Neurology." In addition, each constituent discipline of the ICNS had independent sessions on preselected topics or symposia.

director in an optimum position to be always aware of the status of his program.

Once the selection of authors and discussors had been made, the secretary-general had the responsibility of procuring the texts of presentations which were to be published as abstracts, the complete texts of papers which were to be published as integrated reports, and the texts which were to be ready for simultaneous translations at the sessions. These three types of texts* were indispensable to have, but it was the exception rather than the rule that any author was fully cooperative in this respect. The frequent submission of unfinished papers compelled us to write numerous and costly letters and, in spite of urgent appeals sent out as early as September 1956, our files were still incomplete in April of 1957. In our opinion, it is imperative to have on hand, in the future, all the texts of communications at least four months before the opening of the congress.

More than half of the texts received were not worded in the native tongue of the author and, consequently, had to be revised. Moreover, in spite of explicit instructions, the bibliographies of many authors had to be corrected. This placed an additional work load on the various editorial committees. Our recommendation to authors wishing to participate in future congresses is that they be sure to submit complete texts. For the Brussels Congress a number of authors submitted preliminary texts which they proposed to complete on the galley proofs, and sometimes they ended up by submitting an entirely different text. All this added considerably to printing costs.

DIGESTS OF FREE COMMUNICATIONS

The methods proposed in 1955 for controlling the number of free communications proved to be ineffective. All the national committees, except one, did not grade free communications according to quality, nor did they recommend that any be rejected. Some free communications were submitted without even having passed through their national committees. Because of the diversity of the subjects which were of interest to the various disciplines at the Brussels Congress, the free communications encompassed a very wide variety of subjects. These emergencies which were anticipated in 1955 led the secretary-general to devise a system of digest reporting.**

The free communications which were relevant to a central topic were submitted to the appropriate topic directors, who decided whether to place them on their programs or refer them to one or another of the specially qualified authorities selected as digest leaders. To avoid offending anyone, some topic directors preferred to give these authors a short period on their programs. While this procedure was generally acceptable, it was not, in our opinion, entirely satisfactory. The purpose of a digest is not only to cite briefly an author who cannot be called on to speak because of the large number of free communications, but also to point out what new ideas he proposes or in what way he confirms or invalidates previous findings; slanted in this way, the digest unfolds, in a critical and provocative fashion, our expanding knowledge as well as the content of the communications.

The quality of some of the digests aroused a timely interest, which, of course, presupposes a judicious selection of the digest leader. Digest leaders were selected from among those who knew the particular problems to be presented, but who belonged to different geographic or cultural groups. Some of the free communications, however, were so heterogenous that the digest leader could not master all of them. In these instances, it was found advisable to let the authors themselves speak briefly on aspects of their material which were distinctly beyond the range of competence of the digest leader.

An alternative solution for the future would be to present digests of all presentations dealing with a central theme and of all the free communications which could be classified into homogenous groups, and to allow the authors themselves to present the free communications

*The ICNS publications delivered at Brussels comprised the following volumes: abstracts of reports and communications, two volumes of the formal papers on topics of common interest, and four volumes containing the formal presentations from the sessions of the constituent congresses.

**Time did not permit the authors of free communications to read them at the Brussels Congress. These were grouped according to subject matter and assigned to a digest leader who had the responsibility of synthesizing and presenting the substance of all papers assigned to his group. The names of all authors and co-authors of free communications were mentioned, abstracts of their presentations were published, and, when time permitted, they were invited to explain the text and participate in the discussions.

of a heterogenous character during the last days of the congress so that they could be read before smaller audiences.

DEMONSTRATIONS AND EXHIBITS

In order to permit a digest leader or a topic director to apportion his time judiciously, it is essential that the authors, when submitting papers, give the secretariat full details on slides, films, and any special technical features which any of their visual aids might present. It is also important to use projection material of standard dimensions expressed in international standard units, and to supply the chairmen of the exhibit committees specific data on the linear measurements required for wall or projection surfaces.

In the use of visual aids, two types of material can be distinguished: 1) indispensable material which should be shown in the course of the presentation of a topic; and 2) dispensable material which can be demonstrated after this presentation at a special session, for example, a motion picture or a scientific display. These special sessions should be organized ahead of time and not at the last minute, as was done in Brussels. Under these circumstances, the author should arrange to demonstrate his material at scheduled times when he himself would be present to answer questions. This objective was partially accomplished at Brussels.

In spite of the full program at the ICNS in Brussels, time limits set for sessions were respected, on the whole. All visual aids and graphic material were projected or displayed on time.

REPORTS AND FLOOR DISCUSSIONS

Purely oral presentations, in our opinion, are destined in future congresses to be deemphasized in favor of more documentary presentations, which is certainly for the good. If a participant submits in advance an abstract of 500 to 1,500 words, he knows the essence of what he is going to say. He still can, if he deems it necessary, refresh his orientation by reading his entire report from the volumes which are given to him on his arrival at the congress. A drastic reduction of the purely oral communications would permit more short discussions from the floor than were possible at the ICNS, where they were inevitably curtailed to the disappointment of many.

This diminution of free discussions from the floor may not be as serious as some believe, however. Many participants whose personal views merited recognition were invited to attend the congress as discussors. In former congresses, it was noted that many discussors from the floor merely repeated what they already had written in a previous publication or simply gave a resume of a paper they intended to give later elsewhere. The consensus at Brussels was that the reduction in free discussions, with few exceptions, was not a great loss to the congress. Large congresses are not suitable for the meticulous discussion so frequently found in small highly specialized symposia.

PROBLEMS OF LANGUAGE AND OF ORIGINALITY

Another difficulty in the administration of international congresses concerns the problem of languages. Practically speaking, a simultaneous translation cannot be made in more than three languages in one auditorium or in more than two languages in another. The costs entailed are too great.

If the language of the host country is accepted as the primary official language of a congress, it is not essential to establish scientific liaisons to add to the official working languages (English, German, French) the languages of other countries merely to satisfy national pride, even though these countries are important numerically. The same principle obtains for the number of languages used in the printed abstracts. Printing in more than one language adds to publication costs without providing a corresponding reward to the reader.

Another factor which burdens a congress unnecessarily and which requires appropriate action is that many communications and demonstrations are mere repetitions of studies already published, or films and graphic displays which have been shown elsewhere or have been previously published. The secretary-general should have absolute authority to exclude any communication or presentation which is not original, except under the most extenuating circumstances. This may seem like drastic action, but it is the only way to cope

with the abuse and lack of tact manifested at these congresses by certain participants.

FUTURE NEUROLOGIC CONGRESSES

The desirability of continuing combined international congresses of several neurologic disciplines, held in the same place and at the same time, with provision for joint sessions, was acknowledged by all the constituent congresses represented at the ICNS in Brussels, except the Congress of Neurological Surgery. Most disciplines considered it a real need. However, this does not imply that a combined congress as inclusive as the one held in Brussels should be repeated regularly every four years. The next meeting of an international congress of neurologic sciences should be contemplated when new problems in neurology and in neurologic science have matured sufficiently to justify another combined congress of all disciplines. The interval between congresses need not be regular or fixed far in advance.

To decide when neurologic disciplines are again ready to convene in a combined congress, we must rely on the liaison committees of the various world federations of neurologic disciplines. It was decided in Brussels that the next International Congress of Neuropathology would meet in Munich in the second week of September 1961 and that the Seventh International Neurological Congress would take place in Rome during the third week of September 1961; these two congresses may have one day of joint sessions. The next International Congress of Electroencephalography and Clinical Neurophysiology will meet either before or after the third week of September 1961 and will also endeavor to have a day of joint sessions with the neurologic congress. The Second International Congress of Neurological Surgery will be held during the same year in Washington, D.C.

We may envisage the organization of a Second International Congress of Neurological Sciences to be held in the United States in 1965, if the World Federation of Neurology, which has just been created, has developed the necessary facilities by that time.

This paper was translated from the original French by Dr. Pearce Bailey, Washington, D.C.

■ Tetanus is not a malady peculiar to any country, or climate, or people, but it is more common in hot countries than in cold. It would appear, also, that negroes are more likely to be attacked than whites. Great atmospheric changes, especially from heat to cold and damp, as to a cold and dewy night after a sultry day, are evidently most favorable to the development of tetanus, and so in a less degree are foul air, despondency, terror, physical exhaustion. It must be confessed, however, that cases of idiopathic tetanus, as compared with those which are traumatic, or partly idiopathic and partly traumatic, are, to say the least, extremely rare in this country.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves,* published in 1871.

Production of basal ganglia lesions by chemopallidectomy

Irving S. Cooper, M.D. and Gonzalo J. Bravo, M.D.

DURING THE DEVELOPMENT of the technic of chemopallidectomy for the relief of tremor and rigidity of parkinsonism, it has become evident that not only must one be accurate in the placement of the intracerebral lesion either in the globus pallidus or ventrolateral nucleus of the thalamus, but also one must produce a large circumscribed well-localized lesion in either or both of these areas. Our own attempts with electrocoagulation, radio frequency coagulation, and incisional lesions failed to produce an area of destruction of sufficient size to completely relieve contralateral tremor and rigidity. On the other hand, the use of absolute alcohol by the technic which we have developed will produce in all cases in which it is properly followed a circumscribed, completely localized lesion of whatever size the surgeon wishes to make. Only in this way have we been able to develop a technic by which the lesion could be tailored to the needs of the individual patient.

Very early during the development of this technic it became obvious to us that one technical difficulty to overcome was the possibility of reflux of the neurolytic agent along the needle tract. By staining alcohol with Pantopaque, we have been able to follow the lesion roentgenographically, and it was proved in some of our early cases that reflux did occur occasionally along the needle tract. For that reason a special cannula with a double lumen was developed. One of the lumina leads to a small inflatable balloon at the end of the cannula, while the other lumen is used for injection directly into the brain.

When the cannula has been placed in the brain, the small balloon is inflated by injecting 0.25 to 0.5 cc. of Hypaque into it. This serves two purposes: 1) In the conscious alert patient it produces a reversible lesion so that one can gauge the effect in the contralateral extremities. When this balloon has been inflated in the proper place, tremor and rigidity of the contralateral extremities are immediately alleviated, thus providing an important clinicophysiologic test. 2) Allowing this balloon to remain inflated in situ for 12 or more hours produces a small cavity into which the alcohol-Pantopaque mixture is injected subsequently. Injection of the mixture into this cavity forms a small nidus for subsequent injections over the next several days. These injections, if done carefully, will invariably produce the well localized circumscribed lesion of sufficient size for production of the clinical result desired.

In our experience the single most common cause for incomplete results with this type of operative procedure is the failure of production of a sufficiently sized lesion. This technic makes possible a sufficiently sized lesion in a circumscribed well localized fashion in a conscious, cooperative patient. Moreover, the clinical status of the patient and degree of relief of tremor and rigidity can be compared daily with the roentgenographic appearance of the lesion as it is seen in the accompanying figures.

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This work supported by grants from the Office of Vocational Rehabilitation, Sister Elizabeth Kenny Foundation, Albert and Mary Lasker Foundation, and the Allen P. and Josephine Green Foundation.

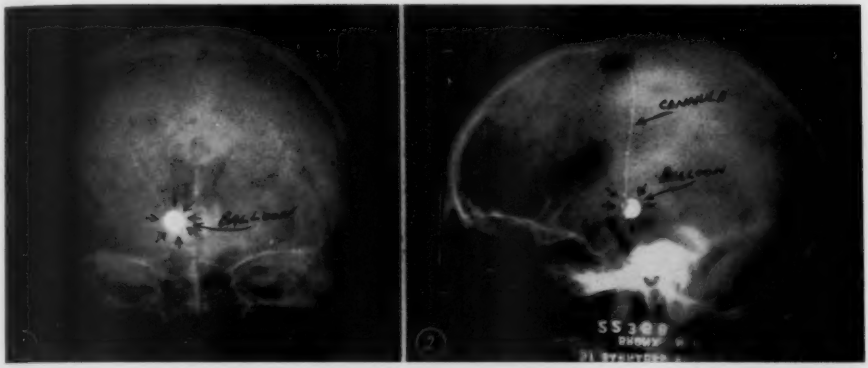

FIG. 1. Anteroposterior roentgenogram made during operation, showing the balloon at the tip of the cannula after it has been inflated with 0.5 cc. of Hypaque. Inflation of the balloon produced alleviation of contralateral symptoms in the conscious patient.

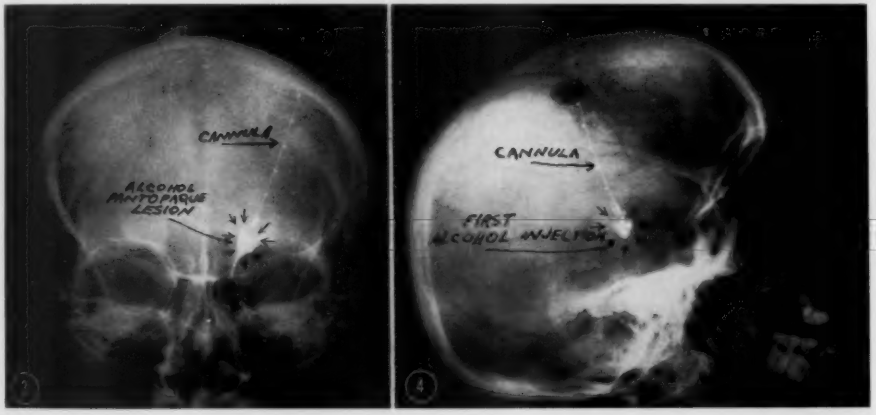

FIG. 2. Lateral roentgenogram, demonstrating polyethylene cannula and inflated balloon in the brain.
FIG. 3. Anteroposterior roentgenogram made during postoperative period. Cannula remains in place but the balloon has been deflated; 0.5 cc. of alcohol-Pantopaque mixture has been injected. The localized lesion produced by this initial injection is visible.
FIG. 4. Lateral view of cannula and lesion demonstrated in figure 3.

Housepian and Guzman-Lopez[1] recently reported on their failure to produce such lesions, citing a total experience of six cases. Referring to the available literature[2–7] on the correct method of production of a well circumscribed lesion in chemopallidectomy, however, we feel certain that this technic can provide successful results. Our experience with this technic in more than 700 operations, 100 animal experiments, and 60 cadaver operations shows that we are now able to produce a sufficiently sized, circumscribed lesion in the globus pallidus or ventrolateral nucleus of the thalamus often enough to effect alleviation of tremor and rigidity in more than 75 per cent of cases.

We would caution those who wish to follow this particular technic not to expect to achieve complete success immediately. In our experi-

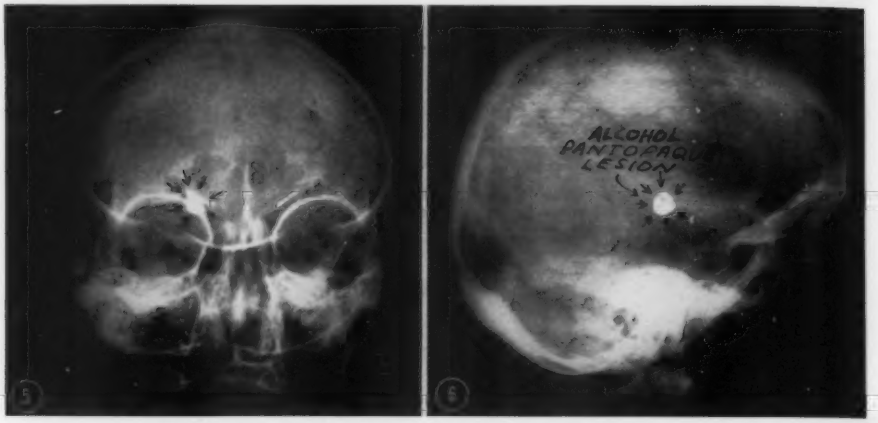

FIG. 5 and 6. Final lesion produced by chemopallidectomy. Note its circumscribed character. It is necessary to produce lesions of this size in order to relieve contralateral extrapyramidal hyperkinesis. The woman in whom this lesion was produced was relieved of contralateral tremor, rigidity, and deformity of many years' duration.

ence one does not become expert even in arteriography during the first few attempts. However, utilization of the presently available anatomic, roentgenographic, and technical reports on this procedure will help to produce the type of lesions shown in the accompanying figures and thereby duplicate the results which we have documented in our own series.

REFERENCES

1. HOUSEPIAN, E. M., and GUZMAN-LOPEZ, M.: Dispersion of fluid materials in intracerebral injections: General observations in conjunction with injection lobotomy and chemopallidectomy. Neurology 7:763, 1957.
2. COOPER, I. S.: Intracerebral injection of procaine into the globus pallidus in hyperkinetic disorders. Science 119:417, 1954.
3. COOPER, I. S.: Chemopallidectomy: An investigative technique in geriatric parkinsonians. Science 121:217, 1955.
4. COOPER, I. S., and POLOUKHINE, N.: Chemopallidectomy: A neurosurgical technique useful in geriatric parkinsonians. J. Am. Geriatrics Soc. 3:839, 1955.
5. COOPER, I. S.: The Neurosurgical Alleviation of Parkinsonism. Springfield, Illinois, Charles C Thomas, Publisher, 1956.
6. COOPER, I. S., and POLOUKHINE, N.: The globus pallidus as a surgical target. J. Am. Geriatrics Soc. 4:14, 1956.
7. BRAVO, G., and COOPER, I. S.: Chemopallidectomy—Two recent technical additions. J. Am. Geriatrics Soc. 4:651, 1957.
8. COOPER, I. S.: Relief of juvenile involuntary movement disorders by chemopallidectomy. J.A.M.A 164: 1297, 1957.

■ The celebrated Dr. Whytt, in his book on nervous diseases, remarks, "that there are few disorders which may not in a large sense be called nervous." He confines himself, however, to the consideration of "those which, in a peculiar sense, deserve the name; inasmuch as they are owing to an uncommon delicacy, or unnatural sensibility of the nerves."

In this publication, I propose to treat of those diseases which consist in, or depend upon, a more general affection of the powers of sensation and motion, particularly *Apoplexy, Palsy,* and *Epilepsy.*

John Cooke in *A Treatise on Nervous Diseases,* published in 1824.

Paresis and hyperexcitability in adynamia episodica hereditaria

Fritz Buchthal, M.D., Lise Engbaek, M.D. and Ingrid Gamstorp, M.D.

RECENTLY a hereditary disease characterized by transient paralysis has been described[1–3] which deviates from the classic familial periodic paralysis. Gamstorp[2] has collected genetic and clinical data from 138 patients with this disease, termed by her "adynamia episodica hereditaria." The most striking difference from the classic form of familial periodic paralysis is the increase in serum potassium accompanying the attacks. Accordingly, administration of potassium precipitates the attacks in episodic adynamia, while it controls the attacks in periodic familial palsy. Other distinguishing features, such as mode of inheritance, age at onset of the disease, frequency and duration of the attacks, and precipitating factors have been described by Gamstorp.[2]

The present study deals with electromyographic findings and the effect of intra-arterial injections of acetylcholine during and between attacks. The pathologic physiology of the disease is discussed in relation to these findings.

MATERIAL AND METHODS

Six patients, a female 38 and five males 11, 21, 33, 53, and 61 years of age, were studied electromyographically during and between attacks. The effect of acetylcholine during and between the attacks was studied in two of these patients (the female and a 21 year old male) and in three additional patients between the attacks only (two females 28 and 23 and one male 26 years of age). The attacks were provoked by oral administration of 2.5 to 5 gm. of potassium chloride in four patients; in two subjects an attack occurred during rest after physical exertion.

Electromyography

The muscle action potentials were led off by means of concentric needle electrodes. Details of the recording technic have been reported.[4]

The action potential pattern was recorded at maximum voluntary effort to determine the type and degree of paresis and at a force allowing discrimination of the individual action potentials to determine the total duration, amplitude, and shape of the potentials. For obtaining mean values of action potential duration the three electrodes were inserted at random into the muscle, and 30 to 60 different action potentials were recorded from 20 to 30 different points. To ensure that the potentials picked up by the electrodes originated from different fibers, the electrodes were advanced in steps of at least 3 mm. The values of duration are compared with those of normal subjects of the same age.[5]

The degree of electrical activity at maximum effort was defined according to the following criteria:

1) Interference pattern (I); simultaneous activity of numerous motor units in which the frequency or amplitude of the individual motor unit discharge cannot be discriminated.

2) Mixed pattern (M); the activity of one or two motor units can be distinguished against a background of activity from more distant units.

3) Single oscillations (SO); the activity of a single motor unit is recorded without interference from the responses of adjacent motor units.

Muscle force was estimated according to the standard routine of the Children's Medical Center in Boston.[6]

Propagation velocity

The propagation velocity of the action potential along the fibers of the muscle was determined by stimulating locally at threshold intensity through a bipolar electrode inserted in the distal portion of the brachial biceps.[7] The propagation velocity was then calculated from the arrival time of the action potentials

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This study was supported in part by a grant from the Muscular Dystrophy Associations of America, Inc.

TABLE 1

ELECTROMYOGRAPHIC FINDINGS IN ADYNAMIA EPISODICA HEREDITARIA

(m. biceps brachii, 36-37° C.)

	Age in years	Muscle force[1]	Attack provoked by[2]	Spontaneous activity	Action potential pattern at maximum effort[3]	Mean action potential duration msec.	Number of different action potentials	Mean action potential duration in normal muscle of the same age msec.	Mean action potential duration in per cent of Duration between attacks	Mean action potential duration in per cent of Duration in normal muscle
Before attack	61	5		++	I	8.7	33	12.2 (10.6-13.8)	100	71
During attack		2–3	R	++	M	7.3	47		84	60
After attack	21	3[4]		(+)	SO-M	8.6	33	8.7 (7.2-10.2)	100	99
During attack		1–2	R	++	SO	6.7	32		78	77
Before attack	11	4		+	I-M[5]	10.3	41	7.8 (6.6-9.0)	100	132
During attack		2	K	O	SO	7.0	45		68	90
Before attack	38	5		O	I	9.5	46	10.8 (9.3-12.4)	100	88
During attack		1–2	K	+	SO	6.9	66		73	64
Before attack	33	5		O	I	10.9	17	10.5 (9.0-12.1)	100	103
During attack		1	K	++	SO	8.8	21		81	84
Before attack	53	5		O	I	12.4	27	11.8 (10.2-13.4)	100	105
During attack		4	K	+	I-M	10.0	24		81	85

[1] 1 = trace, 2 = poor, 3 = fair, 4 = good, 5 = normal

[2] I = interference, M = mixed, SO = single oscillations

[3] R = rest after physical exertion, K = 2.5-5 g potassium chloride (orally)

[4] decreasing degree of paresis

[5] submaximal effort

picked up at three different points over a total distance of up to 10 cm. along the long axis of the brachial biceps. To ensure that the three electrodes recorded potentials from the same fiber or small fiber group, recordings were confined to all-or-none responses of identical threshold containing a steep positive-negative deflection of less than 150 μsec. duration. This indicates that the electrodes are at a distance of less than 0.5 mm. from the active fiber or fiber group.[8] The distance between the tips of the recording electrodes within the muscle was determined as accurately as possible by correcting the distance measured on the skin for the depth and the angle at which the electrodes were inserted into the muscle. The intramuscular temperature was measured by a thermocouple and kept at 36 to 37° C. by means of a heating pad.

Intra-arterial Injection of Acetylcholine

The acetylcholine sensitivity was determined by injecting acetylcholine chloride in varying concentrations into the brachial artery. The amount of acetylcholine solution injected was 2 ml. The procedure has been described previously.[9]

The intra-arterially injected acetylcholine produces vasodilatation in the forearm, and in larger amounts (150-250 μgm. in women, 100-350 μgm. in men[10]) a motor response is obtained, usually flexion of one or more fingers. In the absence of a motor response, vasodilatation indicates that the injection is intra-arterial.

RESULTS

The electromyographic findings are presented in table 1. During the attack of paresis the action potential pattern at maximum effort indicated a substantial reduction in the number of activated muscle fibers, as compared with findings before the attack. This corresponds to the decrease in force estimated by muscle grading. In four of the six patients the electrical activity was reduced so much that the individual action potentials could be discriminated during maximum effort without interference from neighboring fibers, a type of response which otherwise occurs in severe paresis of neurogenic origin or during weak effort in normal muscle. The attack was fur-

thermore characterized by the occurrence of numerous spontaneous potentials in the apparently resting muscle; they had a duration of 2 to 4 msec. and an amplitude of 100 to 200 μV. These potentials were either not present before the attack or occurred much less frequently. The excitability to mechanical stimulation was greatly increased during the attack, as evidenced by the repetitive discharges of action potentials of short duration released by small movements of the needle electrode or by a tap with a reflex hammer.

The mean duration of motor unit potentials recorded at maximum effort during the attack of paresis was 16 to 32 per cent lower than the average duration determined before the attack (table 1). With a mean error of 5 per cent[4] this reduction is statistically significant, a difference of 18 per cent corresponding to 99 per cent significance. The lower mean value of duration was not due to an increased incidence of the short potentials which occurred spontaneously in the apparently resting muscle or were evoked by mechanical stimuli.

The reduction in duration can either be due to a higher rate of propagation of the action potential over the muscle fiber or to a "breaking up" of the motor unit.[5] Since the propagation velocity was normal, the reduced action potential duration must be an expression of a reduction in the number of active fibers within each motor unit.

As to mean action potential duration between attacks, findings were less uniform (table 1). In four patients it was within the limits of the variation found in muscles of normal subjects of the same age. In one patient it was 30 per cent above and in another 30 per cent below the average of normal muscle.

The action potential amplitude was within normal limits. In two cases there was an increased incidence of polyphasic potentials.

The velocity at which the action potential is propagated over electrically stimulated normal fibers is 4 m. per sec. (S.D. 0.4 m. per sec. at 36.5° C.).[7] In different regions of the same muscle it varies about 15 per cent. In three adult patients the propagation velocity was determined before and during an attack. It was 4.6, 4.7, and 4.5 m. per sec., respectively, and remained unaltered during the attack, that is, within the limits of normal muscle. The amplitude of the electrically evoked potentials did not decrease with increasing stimulation frequency up to 50 stimuli per sec.

The five patients examined by intra-arterial injection of acetylcholine had increased sensitivity before and during the attack. A motor response was observed on injection of 50 μgm. in male patients and of 100 μgm. in female patients (table 2). These amounts are below threshold in normals. As in normals the vasomotor response occurred with still smaller amounts of acetylcholine than the motor response.

DISCUSSION

An interpretation of the findings in adynamia episodica presented here must account for the reduction in the number of muscle fibers which can be activated during the attack simultaneously with an increase in excitability. The reduction in muscle force, the occurrence of single oscillations at maximum effort, and the short duration of action potentials are signs of the decrease in the number of active muscle fibers. The spontaneous fibrillations and the readiness to respond to mechanical stimulation, as well as the increase in acetylcholine sensitivity, indicate the hyperexcitability.

TABLE 2

MOTOR RESPONSE TO INTRA-ARTERIAL INJECTION OF ACETYLCHOLINE*

Acetylcholine micrograms in 2 ml.	*Female, aged 38*		*Female, aged 28*	*Female, aged 23*	*Male, aged 21*		*Male, aged 26*
	During attacks	*Between attacks*	*Between attacks*	*Between attacks*	*During attacks*	*Between attacks*	*Between attacks*
20						—	
30							(+)
50	—	+		—	+	+	+
100	+	+	+	+			
150		+					

* normal threshold:[10] females 150-250 μgm. per 2 ml.; males 100-350 μgm. per 2 ml.

The attacks in adynamia episodica are accompanied by an increased serum potassium, and it seemed near at hand to interpret the findings presented in this study on the basis of the effects of high potassium concentrations on muscle membrane excitability. It is well known that a reduction of the ratio of intracellular to extracellular potassium concentration is associated with a decrease in the potential measured across the excitable membrane of the muscle fiber. A moderate reduction in potential enhances the excitability, while a more pronounced reduction of the membrane potential abolishes the conducted response of the muscle fiber.[11] A state of hyperexcitability in some muscle fibers and a block of conduction in others might be caused by an increase in serum potassium, and the symptoms during an attack of adynamia episodica are qualitatively accounted for by the change in serum potassium.

An increase in serum potassium is not the only factor responsible for the attack, however. No increase at all was noted in four attacks and an increase less than 0.5 mEq. per liter was seen in four of 49 attacks studied.[2] An increase of the same order of magnitude as observed during the attack (to maximum 7.3 mEq. per liter)[2] did not produce paresis in normal subjects; ingestion of potassium salts caused serum concentrations up to 7.95 mEq.,[12] 8.6 mEq.,[13] or 7.15 mEq.[14] without muscular weakness. Similarly, the amounts of potassium necessary to provoke an attack in patients with adynamia episodica caused a markedly smaller rise in serum potassium in normals and never produced changes in muscle power.[2] Furthermore, the persistent hyperexcitability between attacks was accompanied by normal serum potassium.

The increase in serum potassium during attacks, which often occurs without administration of potassium, is not preceded or accompanied by a decrease in urinary potassium.[2] This suggests a passing of potassium from the intracellular to the extracellular fluid, or an increased potassium permeability. In this way the ratio of intracellular potassium to extracellular potassium and the membrane potential are further reduced.

Findings with regard to intracellular potassium of muscle in adynamia episodica are somewhat contradictory. In one case[15] the concentration of potassium in muscle between attacks was lower (71.5 mEq. per kg.) than in normal muscle (77 to 112 mEq. per kg.).[16] In the same case the "exchangeable body potassium," which is mainly an expression of intracellular potassium,[17] was reduced from the normal value of 49.3 ± 6.4 mEq. per kg.[18] to 35 mEq. per kg. However, in three other cases from another family there was no significant difference from the normal values and there was a normal rate of exchange between injected potassium and the body potassium.[19] In this connection it is important to realize that only a large reduction in the intracellular potassium concentration produces an appreciable change in the membrane potential. In frog muscle a reduction of the internal potassium concentration by 16 per cent reduced the membrane potential by only 3 per cent (from 91 to 88 mV),[20] a change which is without significant effect on excitability.

Therefore, it is difficult to understand the excitability changes in adynamia episodica in the light of abnormalities in intra- and extracellular potassium concentration only. An additional explanation might be changes in the distribution of sodium and chloride.

No connection was found between the attack of adynamia episodica hereditaria and serum sodium (43 attacks studied) or serum chloride (seven attacks studied).[2] Intracellular sodium and its possible changes during an attack have not been investigated. In two cases of periodic paralysis the sodium balance at the beginning of the attack regularly proved positive, with an abnormal uptake of sodium by muscle and increased serum sodium.[21]

The possibility of a change in chloride permeability in familial periodic paralysis has also been discussed.[22] In the above mentioned case of adynamia episodica described by Liljestrand,[15] the chloride concentration of the muscle was increased from the normal 12.7 to 31.0 mEq./kg.[16] to 40 mEq./kg. This would be consistent with an increase in chloride permeability. With a high chloride permeability, chloride ions may play a significant part in determining the membrane potential.[23] If the chloride ratio is less than the potassium ratio, the membrane potential falls below the equilibrium potential for potassium, resulting

in a net outward movement of potassium.[22] An increase in chloride permeability might in this way contribute to the excitability changes and the high serum potassium observed in adynamia episodica.

It cannot be decided with certainty whether the symptoms are attributable mainly to changes in the neuromuscular junction or in the muscle fiber. However, potassium blocks indirect excitability in lower concentrations than direct.[24] The finding of a normal propagation velocity over the muscle fibers also suggests that the affection manifests itself first at the motor end-plate. A three times normal potassium concentration caused a substantial decrease in the propagation velocity in frog muscle,[25] indicating that higher external potassium concentrations than observed in adynamia would cause more pronounced changes in the muscle membrane.

SUMMARY

The symptoms of adynamia episodica hereditaria differ in several respects from those of classic familial periodic paralysis. One of the most conspicuous differences is an increase in serum potassium accompanying attacks of muscular weakness, provoked by administration of potassium chloride or by rest after physical exertion.

The transient paresis is characterized by a reduction in number of muscle fibers which can be activated, the electromyogram showing a single oscillation pattern at maximum effort and a 16 to 32 per cent reduction in the mean duration of the action potentials.

In addition, there are signs of hyperexcitability during the attack, characterized by spontaneous discharges, increased mechanical excitability, and increased sensitivity to intra-arterially injected acetylcholine.

Between the attacks spontaneous activity was still present, but to a lesser degree. The increased acetylcholine sensitivity persisted between attacks.

The findings are interpreted as a partial depolarization of the excitable membrane, causing a block of some muscle fibers and a hyperexcitability in others. There are indications that the changes appear mainly at the neuromuscular junction.

REFERENCES

1. Sagild, U., and Helweg-Larsen, H. F.: Det kliniske billede ved arvelige transitoriske muskellammelser. Nord. med. 53:981-985, 1955.
2. Gamstorp, I.: Adynamia episodica hereditaria. Acta paediat. Suppl. 108, 1956.
3. Gamstorp, I., Hauge, M., Helweg-Larsen, H. F., Mjönes, H., and Sagild, U.: Adynamia episodica hereditaria. Am. J. Med. 23:385, 1957.
4. Buchthal, F., Guld, C., and Rosenfalck, P.: Action potential parameters in normal human muscle and their dependence on physical variables. Acta physiol. scandinav. 32:200, 1954.
5. Buchthal, F., and Rosenfalck, P.: Action potential parameters in different human muscles. Acta psychiat. et neurol. 30:125, 1955.
6. Hertz, H., Madsen, A., and Buchthal, F.: Prognostic implications of electromyography in acute anterior poliomyelitis. J. Bone & Joint Surg. 36A:902, 1954.
7. Buchthal, F., Guld, C., and Rosenfalk, P.: Propagation velocity in electrically activated muscle fibers in man. Acta physiol. scandinav. 34:75, 1955.
8. Buchthal, F., Guld, C., and Rosenfalck, P.: Volume conduction of the spike of the motor unit potential investigated with a new type of multielectrode. Acta physiol. scandinav. 38:331, 1957.
9. Buchthal, F., and Engbæk, L.: On the neuromuscular transmission in normal and myasthenic subjects. Acta psychiat. et neurol. 23:3, 1948.
10. Engbæk, L.: Acetylcholine sensitivity in diseases of the motor system with special regard to myasthenia gravis. EEG & Clin. Neurophysiol. 3:155, 1951.
11. Jenerick, H. P., and Gerard, R. W.: Membrane potential and threshold of single muscle fibers. J. Cell. & Comp. Physiol. 42:79, 1953.
12. Winkler, A. W., Hoff, H. E., and Smith, P. K.: The toxicity of orally administered potassium salts in renal insufficiency. J. Clin. Investigation 20:119, 1941.
13. Keith, N. M., Osterberg, A. E., and Burchell, H. B.: Some effects of potassium salts in man. Ann. Int. Med. 16:879, 1942.
14. Grob, D., Liljestrand, A., and Johns, R. J.: Potassium movement in normal subjects and effect on muscle function. Am. J. Med. 23:340, 1957.
15. Liljestrand, A.: Fall av adynamia episodica hereditaria. Opuscula Medica, p. 183-193, 1957.
16. Spector, W. S. (editor): Handbook of Biological Data. W. B. Saunders Company, Philadelphia, 1956.
17. Corsa, L., Olney, J. N., Steenburg, R. W., Ball, M. R., and Moore, F. D.: The measurement of exchangeable potassium in man by isotope dilution. J. Clin. Investigation 29:1280, 1950.
18. Sagild, U.: Total exchangeable potassium in normal subjects with special reference to changes with age. Scandinav. J. Clin. & Lab. Invest. 8:44, 1956.
19. Sagild, U.: Personal communication.
20. Adrian, R. H.: The effect of internal and external potassium concentration on the membrane potential of frog muscle. J. Physiol. 133:631, 1956.
21. Conn, J. W., Fajans, S. S., Louis, L. H., Streeten, D. H. P., and Johnson, R. D.: Intermittent aldosteronism in periodic paralysis. Lancet 1:802, 1957.
22. McArdle, B.: Familial periodic paralysis. Brit. M. Bull. 12:226, 1956.
23. Hodgkin, A. L., and Katz, B.: The effect of sodium ions on the electrical activity of the giant axon of the squid. J. Physiol. 108:37, 1949.
24. Coppee, G.: La transmission neuro-musculaire: Curarisation, decurarisation et renforcement a la jonction myo-neurale. Arch. internat. physiol. 53:327, 1943.
25. Buchthal, F., and Engbæk, L.: To be published.

Effects of secondary pallidal and striatal lesions upon cerebellar dyskinesia

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ALTHOUGH the cerebellum is generally regarded as a suprasegmental site of sensory integration outside of the conscious sphere, lesions of the cerebellum and/or its connections usually result in deficits of motor performance. Thus, the cerebellum would seem to serve as an excellent example of the dependence of motor function upon sensory input and integration. Cerebellar deficits, presenting usually as a constellation of intimately related symptoms and signs, must, therefore, represent the substituted inferior functional capacity of the motor system deprived of normal controlling and regulating influences. It would appear that secondary lesions in non-cerebellar structures, known or suspected of contributing to total motor function, might alter or modify the disturbances resulting from cerebellar lesions. The current study was an attempt to explore the physiologic effects of secondary lesions in the globus pallidus and striatum upon cerebellar dyskinesia in monkeys produced by large lesions of the deep cerebellar nuclei.

MATERIAL AND METHODS

Eleven rhesus monkeys weighing between 3,000 and 4,000 gm. were used in this study. Primary lesions of the deep cerebellar nuclei were produced bilaterally by a small glass suction tube introduced into the interior of the cerebellum. Details of this method have been published previously.[3] Animals were observed almost daily and neurologic examinations were made at frequent intervals. Secondary lesions were made after an observation period of at least 20 days after primary surgery. Lesions of the globus pallidus and the striatum were produced by stereotaxic methods.[4] Detailed observations and examinations were recorded following secondary surgery, and cinematographic records were made after both primary and secondary lesions for purposes of comparison.

Animals were sacrificed by perfusion with 500 ml. of 10 per cent neutral formalin under moderate pressure. The brains and spinal cords were further fixed in neutral formalin and later sectioned perpendicular to the axis of the brainstem. The brains and portions of the spinal cords of these animals were impregnated according to the Marchi method and cut serially at 23 μ; every tenth section was mounted. The extent and spatial disposition of the lesions of the deep cerebellar nuclei were estimated at various levels and outline maps were constructed to give data concerning the three dimensional configuration of the nuclear destruction. Attempts were made to arrive at quantitative approximations of the volume of tissue destroyed by the secondary lesions in the globus pallidus and the striatum. Measurements of tissue volume were made according to the method of Dornfeld, Slater, and Scheffé,[10] as in previous studies.[1,2,11]

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OBSERVATIONS

PRIMARY LESIONS

Lesions of the deep cerebellar nuclei in these animals involved various portions of the dentate and interpositus nuclei and were similar to those previously reported[3] with detailed study of associated Marchi degeneration. These lesions differed from those already reported in that primary lesions in some animals (C-2, C-4, C-25, and C-26) involved portions of the brachium conjunctivum as well as the deep cerebellar nuclei. Associated Marchi degeneration of the brachium conjunctivum was essentially the same as reported previously in regard to localization and projection. Although primary lesions occasionally encroached upon the fastigial nuclei, none of the lesions destroyed the roof nuclei. None of these lesions directly destroyed structures within the brainstem, excepting portions of the brachium conjunctivum and the ventral spinocerebellar tracts.

Physiologic disturbances. Primary lesions of the deep cerebellar nuclei produced hypokinesis, ataxia, ataxic tremor, simple tremor, and asynergia. Prior studies[3] have demonstrated that all of these disturbances undergo some degree of attenuation with time, but hypokinesis, ataxia, asynergic disturbances, and ataxic tremor are the most enduring. Simple tremor (tremor at rest) was never seen as an isolated dyskinesia; it was invariably associated with ataxia and ataxic tremor.

Ataxia involved particularly the large muscle masses of the trunk, shoulder, and pelvic girdle. In the upper extremity it appeared most commonly in the form of dysmetria, while in the lower extremity it produced an ataxic gait. Walking and climbing were performed slowly and awkwardly.

Ataxic tremor occurred during voluntary and associated movement; it was of variable and large amplitude, variable frequency, and had a coarse quality. It was associated with ataxia and asynergia.

Simple tremor often involved the entire body musculature initially, but later involved only the extremities. In the majority of these animals it was seen only in the upper extremities where it involved particularly the muscle groups about the shoulder and arm, so as to give the activity a flexor-extensor pattern at the shoulder and elbow. In some animals the flexor-extensor pattern was associated with alternate supination and pronation of the forearm. Simple tremor had a relatively regular rate of about 5 to 6 cycles per second; it was of small amplitude compared with the ataxic tremor and appeared to be transmitted mechanically to the distal portions of the extremities. When present in the lower extremity, an abduction-adduction pattern was noted in which muscles of the thigh and pelvic girdle participated. In the standing or sitting position tremor was rarely transmitted distally in the lower extremity. Simple tremor persisted in all animals until secondary surgery.

SECONDARY LESIONS

Attempts were made to produce unilateral stereotaxic lesions in the globus pallidus in eight animals and bilateral striatal lesions in three animals.

Pallidal lesions. Localized lesions destroying significant portions of the globus pallidus occurred in four of the eight animals. Lesions were localized almost exclusively to the medial segment of the globus pallidus in three animals (C-25, C-26, and C-30) and involved both pallidal segments in rhesus C-53. Although these lesions were relatively large and produced by multiple electrode placements, only one of them destroyed more than 10 per cent of the total volume of the globus pallidus. Volumetric data concerning the total estimated volumes of the globus pallidus, the volumes of pallidal tissue destroyed, and percentile destruction within the globus pallidus are presented in table 1. In three of the four animals with pallidal lesions, destruction of some fibers of the internal capsule was found. Paresis was detectable in two of the four animals (C-25 and C-53), but persisted only in rhesus C-25. Heavy Marchi degeneration of pallidofugal fibers in the lenticular fasciculus, the ansa lenticularis, and the subthalamic fasciculus was seen in each instance.

In two of the eight animals (C-2 and C-4) lesions were located in the internal capsule at approximately the level of the subthalamic nucleus. Localized degeneration in the corticospinal tract could be followed into the spinal cord, and fibers of the dorsal division of the ansa lenticularis were heavily degenerated in

TABLE 1
SECONDARY LESIONS OF THE GLOBUS PALLIDUS

Animal Number:	*C-25*		*C-26*		*C-30*		*C-53*	
	L	*R*	*L*	*R*	*L*	*R*	*L*	*R*
Volume of the globus pallidus in cu. mm.	201	230	165	167	203	195	157	182
Volume of the globus pallidus destroyed in cu. mm.	14	–	–	18	16	–	4	–
Percentil volume of pallidal destruction	7.1	–	–	10.6	7.6	–	2.7	–
Per cent of lesion in medial segment	100	–	–	100	99	–	66	–
Per cent of lesion in lateral segment	–	–	–	–	1	–	34	–

both of these animals. Approximately 7 per cent of the subthalamic nucleus was destroyed, as well, in rhesus C-4.

In rhesus C-29 the lesion destroyed about 45 per cent of the subthalamic nucleus and most of the fibers contained in the lenticular fasciculus. A few fibers of the adjacent internal capsule were destroyed and caudally the lesion extended into the substantia nigra. In one animal (C-5), no stereotaxic lesion was found on histologic study, due presumably to a faulty electrode or a poor electrical contact.

Striatal lesions. Secondary striatal lesions were produced bilaterally in three monkeys with cerebellar dyskinesia. In two of these three animals lesions were placed in the putamen, while in the third animal lesions involved the head of the caudate nucleus, the anterior limb of the internal capsule, and the putamen. In rhesus C-1 relatively small lesions were found in the dorsolateral portions of the putamen bilaterally. In rhesus C-6 large, asymmetric, but volumetrically equal, lesions destroyed significant portions of the putamen bilaterally without injury to the anterior limb of the internal capsule or encroachment upon the globus pallidus. The total volume of tissue destroyed by these striatal lesions, produced by multiple electrode placements, was estimated to be about 25 cu. mm. on each side. Thus, approximately 3 per cent of the total striatum was destroyed, or about 5 per cent of the putamen.[11] Lesions of the heads of the caudate nuclei and the putamina in rhesus C-3 were slightly asymmetric and large, but volumetrically smaller than those found in rhesus C-6. No Marchi degeneration originating from the striatum was seen as a consequence of these lesions, except for a few small fibers passing towards the pallidum.

PHYSIOLOGIC EFFECTS

Pallidal lesions. Secondary lesions of the globus pallidus did not appear to influence the generalized ataxia exhibited by these animals. The gait remained slow, broadbased, and ataxic. Dysmetria in the upper extremities persisted. The most significant effects of pallidal lesions were upon tremor. Simple tremor completely disappeared contralateral to a left pallidal lesion in rhesus C-53 upon recovery from anesthesia. It was never again seen during the 41 day observation period following secondary surgery. Ataxic tremor was greatly reduced in amplitude, force, coarseness, and frequency of occurrence on the first postoperative day and was absent thereafter. On the first postoperative day there was no evidence of paresis, usually indicated by posture, weakness, or disinclination to use extremities. A feeding preference for the hand contralateral to the lesion was specifically noted. From the second to the sixth postoperative day a slight degree of paresis was detectable on the right in the lower half of the face and in the upper extremity. This slight degree of paresis was considered to be due to localized edema, because of the return of full function. Simple and ataxic tremor persisted in the left extremities for 30 days after secondary surgery and gradually disappeared (50 days after the provocative cerebellar lesions).

In the other three animals (C-25, C-26, and C-30) combined simple and ataxic tremor were present prior to secondary surgery. Simple tremor was particularly prominent in these animals. Following pallidal lesions, contralateral ataxic tremor disappeared, except for an occasional tremor cycle seen during voluntary or associated movement. Simple tremor was reduced in amplitude and frequency of

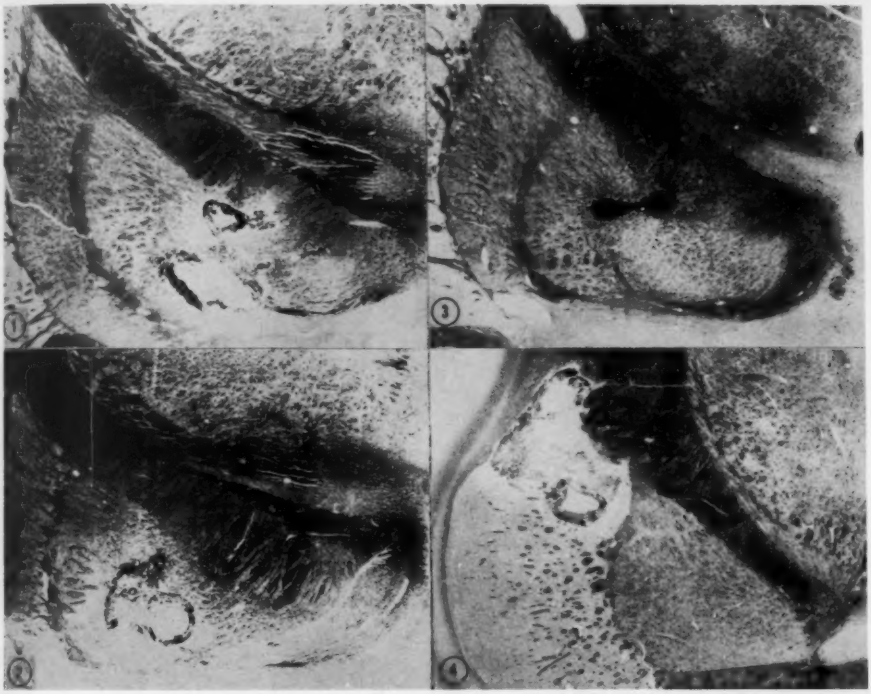

FIG. 1. Rhesus C-25. Photomicrograph of a section showing the secondary pallidal lesions. Approximately 7 per cent of the globus pallidus was destroyed by this lesion which was confined to the medial pallidal segment. Degeneration of fibers in the dorsal and ventral divisions of the ansa lenticularis can be seen. Marchi stain.

FIG. 2. Rhesus C-30. Photomicrograph of secondary pallidal lesion destroying approximately 7 per cent of the structure and provoking heavy Marchi degeneration in pallidofugal fibers. Marchi stain.

FIG. 3. Rhesus C-53. Photomicrograph of secondary pallidal lesion destroying approximately 3 per cent of the globus pallidus. Marchi stain.

FIG. 4. Rhesus C-6. Photomicrograph of secondary stereotaxic lesions in the putamen on the left side. Lesions destroyed approximately 5 per cent of the total volume of the structure. Lesions in this animal were bilateral, simultaneously inflicted, and destroyed about 25 cu. mm. of tissue on each side. Marchi stain.

occurrence, but persisted in this attenuated form until sacrifice. Ataxic and simple tremor ipsilateral to the pallidal lesions appeared to be increased in amplitude and force initially, but after a few days they were the same as prior to secondary surgery. The presence of definite, but minimal, paresis in rhesus C-25 did not affect the pattern or amplitude of the simple tremor contralateral to the pallidal lesion.

Capsular lesions. In two animals (C-2 and C-4) secondary lesions intended for the globus pallidus destroyed significant portions of the internal capsule and provoked heavy degeneration in the dorsal division of the ansa lenticularis. The contralateral extremities were paretic and all tremor, both simple and ataxic, was abolished. Paresis persisted in rhesus C-4 and no recrudescence of tremor was seen. In rhesus C-2 paresis was less marked 14 days after surgery and tremor reappeared contralateral to the lesion. It occurred in bouts of short duration, mostly at rest. Ataxic and simple tremor in the extremities ipsilateral to the

capsular lesions remained unchanged.

In rhesus C-29 ataxic and simple tremor and dysmetria were abolished in the right extremities by a lesion which destroyed approximately 45 per cent of the left subthalamic nucleus and most of the fibers of the dorsal division of the ansa lenticularis. These effects were evident immediately upon recovery from anesthesia and endured until sacrifice 17 days later. No suggestion of paresis was detectable at any time. No choreoid activity was seen following secondary surgery, but on the day of sacrifice a peculiar restlessness was noted in the right foot.

In the animal (C-5) in which a pallidal lesion was attempted but not produced, due presumably to a poor electrical contact, ataxia, asynergia, and combined types of tremor persisted with only slight attenuation for 112 days thereafter.

Striatal lesions. Secondary bilateral striatal lesions in three monkeys (C-1, C-3, and C-6) initially were associated with a modest increase in amplitude, force, and coarseness of prior existing ataxic tremor. Simple tremor was perhaps a little more frequent in appearance, but the pattern was unchanged. Ataxia appeared to be slightly increased, though this may have been due to the fact that these animals were not as profoundly hypokinetic as after primary surgery. These alterations of cerebellar dyskinesia were transitory, lasting five or six days. After this interval the animals appeared the same as before striatal lesions were inflicted.

DISCUSSION

Evidence from basic research and clinical observation indicates that lesions of the globus pallidus can ameliorate and in some instances abolish contralateral abnormal involuntary activity. At the experimental level[5] it has been shown that choreoid hyperkinesia in the rhesus monkey provoked by discrete lesions of the subthalamic nucleus can be reduced and/or abolished by lesions of the globus pallidus which destroy approximately 10 per cent of the total volume of the globus pallidus. The most effective lesions are those localized to the medial segment of the pallidum. The physiologic effect of lesions in the medial pallidal segment is quantitatively greater than that resulting from lesions in the lateral pallidal segment, because a greater number of pallidofugal fibers are interrupted. Clinical observations[7,8,12] indicated that pallidal lesions, produced by a variety of surgical technics, not only ameliorate the tremor and rigidity associated with paralysis agitans, but also may be effective in controlling dyskinesia associated with athetosis, ballism, chorea, and dystonia.[9] An adequate explanation as to why pallidal lesions favorably affect dyskinesia is still being sought. It would seem that a certain degree of pallidal function must be preserved in all of these pathologic conditions and that dyskinetic phenomena are to some extent dependent upon this. From an anatomic point of view, the globus pallidus appears to be a focal structure upon which a number of pathways concerned with nonpyramidal motor function converge. Most of the centrally directed fibers originating in the striatum pass medially to, or through, the globus pallidus. The subthalamic nucleus projects and receives fibers from the globus pallidus by way of the subthalamic fasciculus. Fibers originating from part of the dentate nucleus[3] and localized to the ventral part of the brachium conjunctivum enter the globus pallidus by way of the dorsal and ventral divisions of the ansa lenticularis. Thus, the globus pallidus would seem to be capable of serving as a principal site of integration for motor activity. The manner in which pallidal impulses ultimately reach segmental levels is unknown and undoubtedly is indirect and complex.

The current study was concerned with the physiologic effects of pallidal and striatal lesions upon cerebellar dyskinesia in the rhesus monkey. This study was largely exploratory in nature, but there was reason to believe that secondary pallidal lesions might significantly modify dyskinesia of cerebellar origin. If the basic neural mechanism responsible for tremor of cerebellar origin were in any way similar to that underlying tremor, as seen in disease of the basal ganglia, ameliorative effects might be expected.

Carrea and Mettler[6] studied the effects of striatal lesions upon dyskinesia resulting from lesions of the brachium conjunctivum in the monkey. In most instances lesions were not restricted to either the striatum or the bra-

chium conjunctivum, making interpretation of results extremely difficult. They concluded that striatal damage may convert a silent brachial lesion into an overt physiologic deficit. The protocols seemed to indicate that secondary striatal lesions produced an exaggeration of cerebellar dyskinesia.

The results of this exploratory study indicated that secondary lesions of the globus pallidus reduced the severity of contralateral tremor due to cerebellar lesions. Ataxic type tremor appeared to be ameliorated to a greater extent than simple tremor (tremor at rest). If these animals had exhibited exclusively ataxic tremor prior to pallidal lesions, this result might have been interpreted as a conversion of ataxic tremor to simple tremor. This was not the case, since simple tremor was present prior to placement of pallidal lesions, and it persisted after such lesions in an attenuated form. Generalized ataxia and asynergic disturbances were not significantly affected by the secondary pallidal lesions. The effect of pallidal lesions was crossed.

Lesions of the internal capsule eliminated tremor, reduced asynergic disturbances contralaterally, and produced paresis. Since these lesions also interrupted pallidofugal fibers contained in the dorsal division of the ansa lenticularis, this effect cannot be attributed entirely to corticospinal injury. Elimination of all tremor contralateral to a lesion of the dorsal division of the ansa lenticularis in rhesus C-29 strongly suggested that the latter structure may be particularly important in the mechansm of cerebellar dyskinesia. This case confirmed previous findings that preservation of the fibers of the dorsal division of the ansa lenticularis is as essential for the production of subthalamic hyperkinesia as destruction of an adequate volume of the corpus Luysii.

Striatal lesions produced only transitory alterations of pre-existing cerebellar dyskinesia which did not seem significant.

SUMMARY AND CONCLUSIONS

An attempt was made to determine the physiologic effect of secondary pallidal and striatal lesions upon cerebellar dyskinesia in 11 rhesus monkeys. Primary lesions of the deep cerebellar nuclei destroying portions of the dentate and interposed nuclei provoked hypokinesis, ataxia, asynergic disturbances, ataxic tremor, and simple tremor. After an observation period of at least 20 days, attempts were made to produce unilateral stereotaxic lesions in the globus pallidus in eight monkeys and bilateral striatal lesions in three monkeys. Unilateral secondary lesions were localized to the globus pallidus in four animals, to the internal capsule in two animals, and involved the dorsal division of the ansa lenticularis and the subthalamic nucleus in one animal. Striatal lesions were found in the heads of the caudate nuclei in one animal and in the putamina in two animals. Cinematographic records were taken of all animals after primary and secondary lesions. Detailed histologic study of the lesions and the resulting degeneration was made from serial Marchi-stained sections.

The following conclusions were drawn from this study:

1. Ataxic and simple tremor in the rhesus monkey provoked by partial lesions of the dentate and interposed nuclei are reduced in amplitude, force, coarseness, and frequency of occurrence by contralateral lesions of the globus pallidus.

2. Secondary lesions of the globus pallidus in the rhesus monkey appear to be more effective in ameliorating ataxic tremor than simple tremor.

3. Secondary unilateral lesions in the rhesus monkey destroying less than approximately 10 per cent of the volume of the globus pallidus do not appear to modify ataxia or asynergic disturbances due to primary cerebellar lesions.

4. Electrolytic lesions of the internal capsule interrupting fibers of the dorsal division of the ansa lenticularis abolish contralateral tremor and produce paresis.

5. Ataxic and simple tremor in the rhesus monkey resulting from lesions of the deep cerebellar nuclei may be abolished by lesions of the contralateral lenticular fasciculus.

6. Bilateral secondary striatal lesions produce no significant alteration of pre-existing cerebellar dyskinesia in the rhesus monkey.

The hypothesis is presented that some of the dyskinetic manifestations of cerebellar deficit are dependent upon the integrity of the globus pallidus and its efferent fiber systems.

REFERENCES

1. Carpenter, M. B.: A study of the red nucleus in the rhesus monkey. Anatomic degenerations and physiologic effects resulting from localized lesions of the red nucleus. J. Comp. Neurol. 105:195, 1956.
2. Carpenter, M. B., and Carpenter, C. S.: Analysis of somatotopic relations of the corpus Luysii in man and monkey. Relation between the site of dyskinesia and distribution of lesions within the subthalamic nucleus. J. Comp. Neurol. 95:349, 1951.
3. Carpenter, M. B., and Stevens, G. H.: Structural and functional relationships between the deep cerebellar nuclei and the brachium conjunctivum in the rhesus monkey. J. Comp. Neurol. 107:109, 1957.
4. Carpenter, M. B., and Whittier, J. R.: Study of methods for producing lesions of the central nervous system with special reference to stereotaxic techniques. J. Comp. Neurol. 97:73, 1952.
5. Carpenter, M. B., Whittier, J. R., and Mettler, F. A.: Analysis of choreoid hyperkinesia in the rhesus monkey. Surgical and pharmacological analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of Luys. J. Comp. Neurol. 92:293, 1950.
6. Carrea, R. M. E., and Mettler, F. A.: Function of the primate brachium conjunctivum and related structures. J. Comp. Neurol. 102:151, 1955.
7. Cooper, I. S.: Surgical alleviation of parkinsonism; effects of occlusion of the anterior choroidal artery. J. Am. Geriatrics Soc. 2:691, 1954.
8. Cooper, I. S.: Neurosurgical Alleviation of Parkinsonism. Charles C Thomas, Springfield, Illinois, 1956.
9. Cooper, I. S.: Relief of juvenile involuntary movement disorders by chemopallidectomy. J.A.M.A. 164: 1297, 1957.
10. Dornfeld, E. J., Slater, D. W., and Scheffe, H.: A method for accurate determinations of volume and cell numbers in small organs. Anat. Rec. 82:255, 1942.
11. Harman, P. J., and Carpenter, M. B.: Volumetric comparisons of the basal ganglia of various primates including man. J. Comp. Neurol. 93:125, 1950.
12. Narabayashi, H., Okuma, T., and Shikiba, S.: Procaine oil blocking of the globus pallidus. Arch. Neurol. & Psychiat. 75:36, 1956.

When epilepsy is preceded or accompanied by the sensation called aura epileptica, a nerve in the part from which the aura proceeds is sometimes found to be diseased. Under these circumstances ligatures have been found successful in preventing a fit; but with a view to a radical cure of the disease, something further should be attempted. The part from which the aura proceeds should be destroyed, when it can be done with safety, by cutting it out, or by the application of an actual or potential cautery. When the part cannot be safely destroyed, we should endeavour to remove the morbid affection in it by blistering, or by establishing an issue upon it. When these measures cannot be executed, or do not succeed, if the disease seems to proceed from the extremity of a particular nerve, which we can easily come at in its course, it will be proper to divide that nerve. Dr. Darwin says, "I once saw a child, about ten years old, who frequently fell down in convulsions, as she was running about in play. On examination a wart was found on one ancle, which was ragged and inflamed, which was cut off, and the fits never recurred."

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Distribution of high energy phosphate in normal and dystrophic muscle

Ethel Ronzoni, Ph.D., Stanley Wald, M.D.,
Leonard Berg, M.D. and Robert Ramsey, M.D.

THE PROOF that creatine of muscle is the precursor of creatinine excreted in the urine was amply furnished by Block and Schoenheimer,[1] using isotopically marked glycine as the precursor of creatine and finding the tracer in equal concentrations in urinary creatinine and muscle creatine. Borsook's[2] very plausible suggestion of the mechanism of the conversion of creatine phosphate to creatinine fits in with the older demonstration of Schafer that creatinine excretion is proportional to the muscle mass. The occurrence of large amounts of creatine and correspondingly reduced amounts of creatinine in the urine of patients with muscular dystrophy indicates that the production of creatine proceeds at a normal rate but the muscles are incapable of holding creatine. The recent work of Benedict and co-workers[3] using N^{15}-marked glycine is interpreted to mean that the newly formed creatine fails to enter the muscle and, therefore, does not mix with the creatine already within the muscle. The N^{15} of the creatinine excreted only very slowly approaches the N^{15} concentration the creatine excreted. Since normal children are forming creatine in excess[4] of that retained by the muscle, it would be feasible to test this point on normal children. It may be that, when creatine is produced in excess of that used by the muscle, it is simply excreted, and only when it is not produced in excess of its use, as in the normal rat of Schoenheimer, does it become completely mixed with the pool of creatine phosphate held within the muscle. This would imply a specific mechanism for the uptake of creatine such as, for example, the phosphorylation of creatine by creatine kinase and adenosine triphosphate.

It was with the idea of elucidating the cause of failure to retain creatine that an analysis was made of the various phosphate compounds related to the formation of creatine phosphate. This report shows that on noncollagen protein basis the creatine phosphate is low and the total creatine is correspondingly reduced in dystrophic muscle. The amount present varies widely in different muscles from 4 to 55 per cent of that contained in normal human muscle. The adenosine triphosphate is frequently normal with respect to the noncollagen protein and is never lowered to the extent observed for creatine phosphate. This indicates that the failure to produce creatine phosphate is not due to the lack of high energy phosphate. A study of the enzymes involved is now in progress.

PATIENT MATERIAL

Muscle samples were obtained from 17 patients and four control subjects. Sixteen of the patients had syndromes of progressive weakness and wasting of the muscles of the girdles and of the proximal portions of the extremities, compatible with diagnosis of progressive muscular dystrophy. None had clinical or laboratory evidence of inflammatory muscle disease (polymyositis). Ten of these patients had histories of relatives affected by a similar illness. The seventeenth patient had a clinical picture typical of myotonic dystrophy. The degree of function disability in each patient was graded according to an arbitrary scheme of +, ++, +++.

Control muscle samples were obtained from otherwise normal individuals undergoing orthopedic operations. The control subjects were all adults. In two cases where bone transplants were done for spinal fusion, gluteus maximus and back extensors were both biopsied in the same individual.

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METHOD OF HANDLING THE MUSCLE

In the subjects under study, the muscle to be used was exposed under local anesthesia (procaine without adrenalin). Care was exercised to avoid infiltration of the muscle area to be excised. The part to be used was then carefully and rapidly dissected out and immediately dropped into liquid nitrogen. The procedure took variable lengths of time. In general, from 30 seconds to two minutes were required from the time the cutting of the muscle was started until it was frozen. The muscle was kept in liquid nitrogen until the experimental procedures were started from 30 minutes to an hour later.

Biopsies from control subjects were taken under general anesthesia (ether) and were treated in the same way as the biopsy material from patients.

Without thawing, the muscle was crushed in a mortar composed of a stainless steel centrifuge tube, with an accurately fitted plunger made of the same material. Both the mortar and plunger were chilled with liquid nitrogen and packed with dry ice. By pounding with a hammer the whole of the muscle could be crushed to a pulverized state. The pulverized muscle was transferred to a chilled 50 cc. glass centrifuge containing 6 per cent ice cold trichloroacetic acid and made to a volume 20 times the weight of the original muscle. After thoroughly mixing and waiting for the muscle to thaw, the precipitated protein was centrifuged in the cold. In many dystrophic muscles of high fat content there was some floating material on top, but it was always possible to remove 2 cc. with a pipette for the determination of inorganic phosphate, creatine phosphate, total phosphate, and total creatine. The determination of inorganic phosphate and creatine phosphate was made immediately.

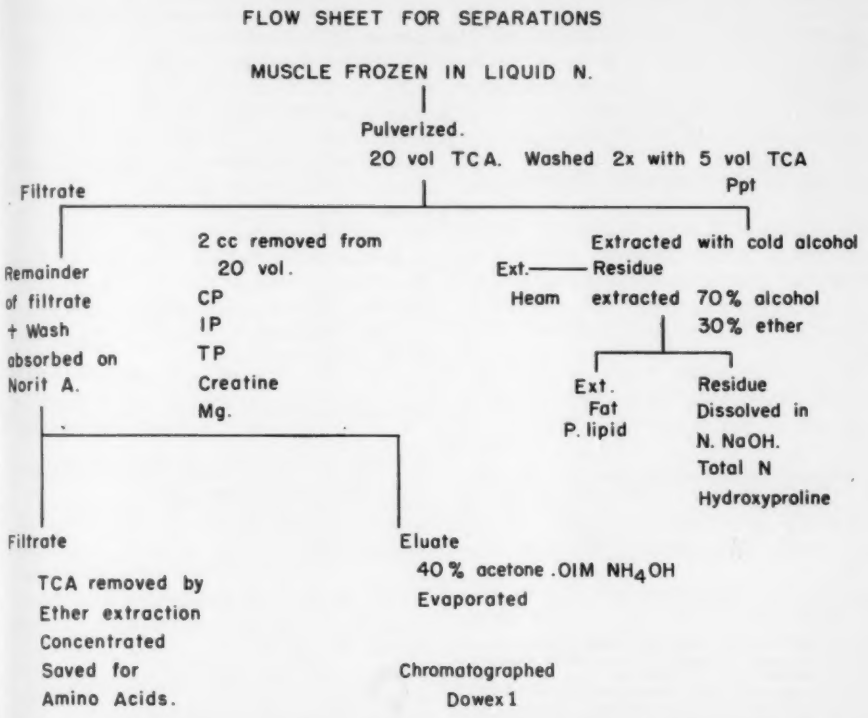
The remaining supernatant was filtered and the precipitate washed twice with five volumes of trichloracetic acid centrifuged and filtered through the same paper. The combined filtrates were used for the nucleotide fractions.

Any particles were returned to the centrifuge tube and extracted with cold alcohol, which removed the trichloracetic acid and dissociated the hemoglobin and myoglobin so that the alcohol extract could be used for total heme. Ether and alcohol were used to extract the lipoids. The residual muscle was dissolved in normal sodium hydroxide for 24 hours, centrifuged, and an aliquot removed for determination of total nitrogen. Another aliquot was hydrolized with hydrochloric acid, and hydroxyproline was determined on the hydrolysate. The collagen content was calculated from the hydroxyproline and deducted from the total protein to give values for noncollagen protein. The flow sheet shows in outline this procedure.

METHOD OF ANALYSIS

Creatine phosphate and inorganic phosphate were determined by a modification of the Fiske and Subbarow method[5] devised by Furchgott.[6] The method of Lowry[7] was used for total phosphate. Borsook's[8] procedure was used for creatine and creatinine. Nitrogen was determined by micro Kjeldahl, and hydroxyproline by the method of Neuman and Logan.[9]

The nucleotides were determined by a chromatographic procedure similar to that used by Cohn and Carter.[10] The purine and pyrimidine compounds were absorbed on Norit A and washed with water until the washing was neutral. This filtrate from Norit A contained the amino acids, with the exception of tyrosine and was saved for future analysis. The nucleotides and other compounds were eluted from the Norit with a mixture of 40 per cent acetone in one-tenth molar ammonium hydroxide. This eluate was evaporated to dryness at 20° with a rotary evaporator under vacuum. The residue was taken up in water adjusted to pH 8 with ammonium hydroxide and placed on a column of Dowex 1 x 10 (200-300 mesh.) 1 cm. in diameter and 5 cm. long. All of the eluent was collected in 15 cc. aliquots. In the following order the eluents were 75 cc. water, 300 cc. 0.002 M hydrochloric acid, 300 cc. 0.003 M hydrochloric acid, followed by a constant gradient elution in which 500 cc. 0.003 M hydrochloric acid was mixed with 500 cc. 0.003 M hydrochloric acid containing 0.2 M sodium chloride. The rate of flow was approximately 1 cc. per minute. A syphon collecting device was used to keep the size of aliquots constant. The individual samples were read in the Beckman spectrophotometer at 260 mu and the amount of the various compounds calculated from the absorption.



It was possible to separate adequately by this procedure the following compounds, hypoxanthine, adenylic acid, inosinic acid, adenosine diphosphate, and adenosine triphosphate (figure 1D). When the procedure was applied to extracts of rat muscle, prepared in a manner that would allow some of the breakdown products of adenosine triphosphate to accumulate, the chromatograms showed a rather large amount of ultraviolet absorbing material in the fraction removed by water. Also between hypoxanthine and adenylic acid another peak is present which overlaps the adenylic acid fraction. These are shown in figure 1C.

The water-eluted material appeared to contain some purine compound, but the absorption curve was ambiguous. Rechromatographed on Dowex 50 H^+ cycle, it could be separated into three peaks (figure 2). The first is hardly retained by this column, all being removed in the first three or four fractions. This material has a very atypical absorption curve and was not further investigated. The second peak removed after starting the acid in a gradient elution gave a positive orcinol reaction and contained no phosphate and had an absorption curve of a hypoxanthine compound. This appears to be inosine, but further work will be required for its evaluation. The third fraction which follows inosine is small in amount and has not been identified.

The three compounds removed from the Dowex 1 column with 0.002 M hydrochloric acid can be better resolved by using a gradient elution. Figure 3 shows three peaks adequately separated. The material falling between hypoxanthine and adenylic acid is tentatively identified as diphosphopyridine nucleotide. It gives an orcinol reaction for pentose and has an absorption curve similar to adenine and contains phosphate.

The system of elution adopted, while still not perfect, affords better resolution of the less acidic fractions than does the procedure of

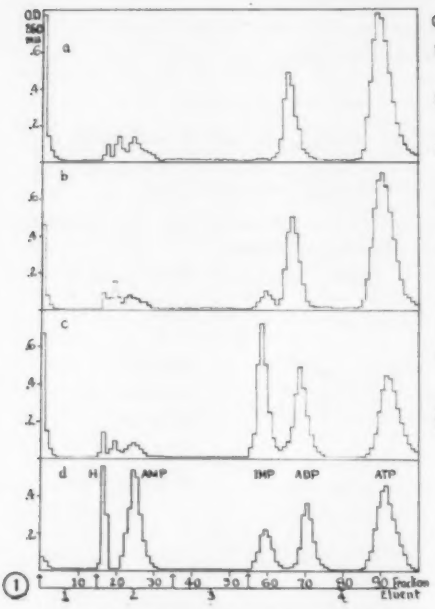


FIG. 1. Chromatograms of extracts from 2 gm. rat muscle. *A*, gastrocnemius carefully dissected without injury. *B*, gluteus maximus cut out. *C*, frozen, pulverized, thawed before precipitation. *D*, known solution as indicated. Eluents (1) H_2O, (2) 0.002 M HCl, (3) 0.003 M HCl, (4) Gradient elution 0.003 M HCl to 0.003 M HCl containing 0.2 M NaCl.

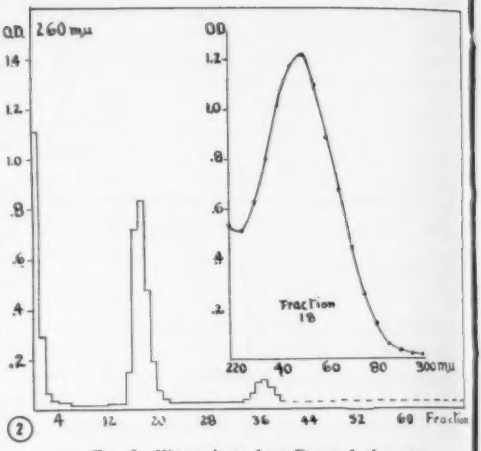


FIG. 2. Water eluate from Dowex 1 chromatographed on Dowex 50 H+ cycle. Inset shows absorption curve of fraction 18.

Cohn and Carter,[10] used by Jordan and Gray[11] for separation of nucleotides in rat muscle.

Since labile phosphate compounds were to be studied, it was necessary to find out if data collected in this manner would have any meaning in the light of the necessary damage to the biopsy muscle in procuring a sample. Therefore, the experimental procedures were duplicated as nearly as possible on rat muscle which could be compared with muscles taken under the best operative condition and without contraction. While damage to muscle induced by cutting lowers slightly the creatine phosphate and increases the inorganic phosphate, it has a rather minor effect. In figure 1B and C it can also be seen that the ratio of adenosine triphosphate to adenosine diphosphate is also somewhat changed, and later inosinic acid appears, depending on the amount of damage. Inosinic acid is lacking in an uninjured muscle.

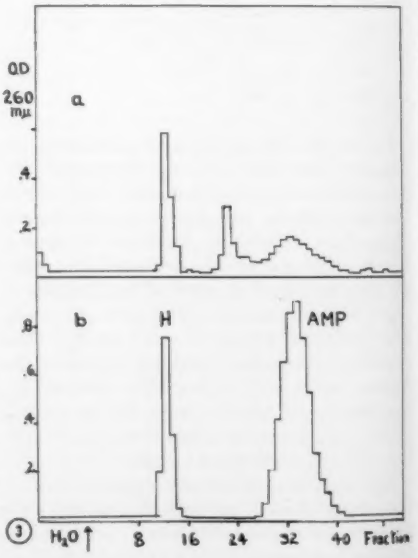


FIG. 3. Gradient elution from Dowex 1 H_2O to 0.002 M HCl. *A*, 0.002 M HCl eluent from muscle extracts. *B*, known hypoxanthine and adenylic acid.

The pattern, however, is quite consistent, the changes are slight, and it seemed highly worthwhile to estimate these values in dystrophic muscle.

The early fractions eluted from the column have not been determined quantitatively, since there is considerable overlapping, the quantities are small, and the error due to the nonspecific absorption would make such values meaningless. That hypoxanthine and adenylic acid, as well as an unidentified substance, is present in all muscle is obvious and must seriously interfere with the values of adenylic acid in normal muscle, as determined by Jordan and Gray.[11] These fractions should enter into the balance sheet of nucleotide distribution and further work is in progress on their quantitative estimation.

PROTEIN CONTENT

The protein content of normal human muscle is approximately 18 per cent of the total wet weight of the muscle and fat content is between 2 and 3 per cent. These values are similar to those reported by Fischer[12] for rat muscle. Based on the probability that collagen and elastin are the only proteins of muscle containing hydroxyproline and that elastin is the small amount of discarded material insoluble in normal sodium hydroxide, the amount of collagen was calculated, using the value of 13 per cent hydroxyproline, as determined by Neuman and Logan.[9] This method gave values for collagen in normal muscle of from 3.3 to 4.3, which are close to other values reported in the literature based on the direct separation of collagen. When the collagen is deducted from the total protein, normal muscle contains from 13 to 14.3 per cent noncollagen protein.

From table 1 it can be seen that in all of the dystrophy cases the noncollagen protein is lower, while the collagen content is higher than in normal muscle. The fat content of the dystrophic muscle is also notably higher and more variable than in the normal muscle.

CREATINE PHOSPHATE

The values for creatine phosphate and creatine based on the noncollagen protein content also shown in table 1 are remarkably constant in normal muscles, the differences between muscles being hardly greater than the experimental error of the method. This is more remarkable when the damage due to cutting the muscle is kept in mind and gives confidence in the low values for creatine phosphate obtained in dystrophic muscles. However, the values for inorganic phosphate recorded in the same table show considerable variation in the dystrophic muscles and are lower than in normals. There is no correlation between the higher inorganic phosphate and lower creatine phosphate values. Indeed, the muscles with the lowest creatine phosphate content tend also to have low inorganic phosphate. The constant ratio (figure 4) between the creatine and creatine phosphate, which is the same as that of normal muscle, is evidence against the probability of any serious loss of creatine phosphate due to the procedure.

The low creatine phosphate of these dystrophic muscles per unit of noncollagen protein is in striking contrast to the values observed in muscles undergoing denervation atrophy. In the latter case, the creatine phosphate remains constant during the progress of atrophy based on the intracellular volume of the muscle.[13] There would appear to be something else involved besides the loss of cellular material which causes a reduction in creatine phosphate.

THE NUCLEOTIDE FRACTION

Figures 5 and 6 show representative chromatograms of normal human and dystrophic muscles. The values plotted are those obtained from extracts of 2 gm. samples. While the pattern is the same for all muscles, the amounts present on a weight basis, represented by the area under the curve, are much lower in the dystrophic muscles. Except for the more frequent occurrence of the inosinic acid peak in dystrophic muscles, there are no qualitative differences. Only one normal muscle out of six studied showed a trace of inosinic acid, while 50 per cent of the dystrophic muscles showed a small amount of this substance. The normal series was taken under general anesthesia with muscles in relaxed condition, while the dystrophic muscles were removed under local anesthesia accompanied by a certain amount of tension and movement. This may account for the difference.

TABLE 1

CREATINE + PHOSPHOCREATINE CONTENT OF MUSCLE AS RELATED TO NONCOLLAGEN PROTEIN

Subject	Protein Noncollagen Wet Weight Per Cent	Protein Collagen Wet Weight Per Cent	Fat Wet Weight Per Cent	Total Creatine per kg. Protein	Creatine Phosphate per kg. Protein	Inorganic Phosphate per kg. Protein	Muscle used
				mM	mM	mM	
Normal							
1	14.0	3.9	3.1	204	115	41.5	erector spinae
	14.3	3.6	2.9	195	125	34.6	gluteus maximus
2	13.8	4.1	1.9	206	139	36.4	erector spinae
	14.2	3.3	2.8	202	118	36.3	gluteus maximus
3	14.4	3.9	3.1	198	135	33.7	erector spinae
4	13.0	4.3	3.3	220	124	35.1	erector spinae
Myotonic dystrophy							
W.D.	12.0	4.0	–	118	82	46.0	quadriceps femoris
Progressive muscular dystrophy							
T.C. 1	6.2	5.7	10.3	34	23	31.2	trapezius
T.C. 2	6.5	5.4	12.6	32	22	30.0	trapezius
L.R. 1	6.7	6.0	7.5	48	33	30.4	trapezius
L.R. 2	6.3	6.8	9.3	52	35	32.5	trapezius
L.J.	8.5	3.8	8.7	66	49	25.2	gastrocnemius
H.G.	7.2	3.6	15.7	112	68	33.0	deltoid
G.F.	8.5	6.1	14.6	170	100	31.0	deltoid
J.McD.	8.7	4.2	7.8	60	41	22.8	gastrocnemius
J.F.	4.3	5.7	23.0	7	5	14.2	deltoid
B.F.	6.3	5.3	9.0	57	38	30.7	gastrocnemius
R.A.	9.0	5.2	–	106	62	28.3	brachioradialis
L.Re.	5.2	5.9	12.9	63	39	35.0	gastrocnemius
J.Re.	3.6	6.7	8.2	21	15	30.1	gastrocnemius
L.W.	5.1	6.9	7.8	9	6	21.1	gastrocnemius
L.M.	3.4	7.3	18.6	32	21	20.8	gastrocnemius
R.McD.	10.5	4.0	11.8	107	68	27.2	gastrocnemius
M.H.	8.4	4.3	6.2	121	71	36.0	gastrocnemius
M.K.	6.5	4.3	10.7	135	79	30.0	quadriceps femoris

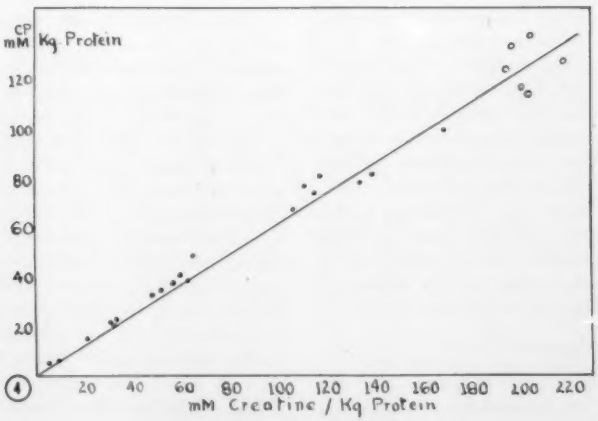


FIG. 4. Relation of creatine to creatine phosphate. Solid dots represent dystrophic muscle. Circles represent normal muscle.

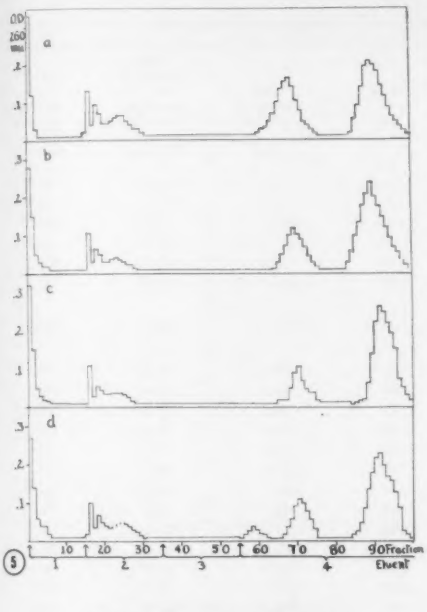


FIG. 5. Chromatograms of normal human biopsy muscle. Eluents as in figure 1.

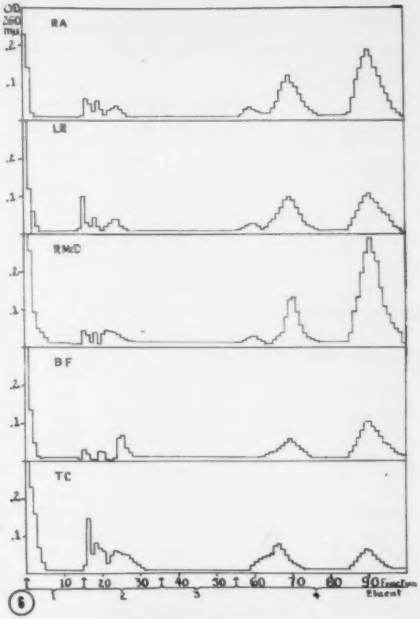


FIG. 6. Chromatograms of dystrophic muscle. Eluents as in figure 1.

In table 2 the amounts of adenosine diphosphate and adenosine triphosphate are related to the noncollagen protein. On this basis the dystrophic muscles approach the normal muscle in content of these two substances. In the more seriously atrophied muscles, however, the values may drop to one-third or one-fourth of that contained in normal muscle. In all cases it will be seen that the energy-rich nucleotides are better maintained than is creatine phosphate. In the muscles which showed practically normal nucleotide, the creatine phosphate was only 45 to 50 per cent of the normal value.

The ratio of adenosine triphosphate to adenosine diphosphate, though somewhat variable in the normal muscles, approaches a value of around 3. In one case where this value was 2.12, inosinic acid was found to be present. In dystrophic muscles there is a wide variation in the ratio from 1.2 to 3.2. The low values are not always accompanied by the appearance of inosinic acid. These low ratios have no explanation at the present time. That the values for adenylic acid and hypoxanthine should be taken into consideration in a complete balance of nucleotide fraction is important, and we are interested in this problem at the present time. From a study of rat muscle under varying experimental conditions, it has been found that one of the first changes to occur in muscle on injury due to cutting or thawing after freezing is a change in the ratio of adenosine triphosphate to adenosine diphosphate, followed by the appearance of inosinic acid and then increased hypoxanthine. So far, no notable change has occurred in the amount of adenylic acid, at least after short periods of treatment. The changes are particularly rapid after freezing and thawing. On the other hand, postmortem changes in uninjured muscle are quite slow but in the same direction.

DISCUSSION OF CASES

A brief summary of the histologic findings and an estimate of functional disability are

TABLE 2

NUCLEOTIDE FRACTIONS AS RELATED TO NONCOLLAGEN PROTEIN

Subject	IMP	ADP per kg.	ATP per kg.	ATP / ADP	High Energy P per kg.	High Energy P Average Normal	CP Average Normal
		mM	mM		mM	Per Cent	Per Cent
Normal							
1	±	24.0	80.0	3.34	184.0	103.5	90.5
	−	25.6	78.4	3.06	182.4	102.8	98.2
2	−	30.2	73.0	2.41	176.0	99.0	109.0
	+	30.2	63.8	2.12	157.8	88.8	92.8
3	−	24.5	78.0	3.18	180.0	101.2	106.5
4	−	26.1	80.2	3.08	186.5	105.0	97.5
Myotonic dystrophy							
W.D.	−	23	80	3.47	183.6	102.5	64.0
Progressive muscular dystrophy							
T.C. 1	−	14.8	26.0	1.86	66.8	37.6	18.0
T.C. 2	−	14.0	26.2	1.86	66.4	37.4	17.3
L.R. 1	+	16.5	30.3	1.81	77.1	43.2	26.0
L.R. 2	+	16.7	31.0	1.85	78.7	43.8	27.5
L.J.	−	26.0	52.0	2.00	130.0	73.0	38.5
H.G.	−	20.2	62.0	3.09	123.0	69.4	53.5
G.F.	−	21.7	69.5	3.17	160.7	90.0	78.6
J.McD.	−	17.1	33.0	1.94	83.1	46.7	32.3
J.F.	−	10.6	20.3	1.88	51.2	29.0	3.9
B.F.	−	12.2	32.4	2.62	77.0	43.0	29.8
R.A.	+	24.7	64.1	2.67	152.9	86.0	48.8
L.Re.	−	23.8	49.5	2.08	122.8	68.6	30.7
J.Re.	+	12.7	36.0	2.83	84.7	47.5	11.8
L.W.	+	12.2	15.5	1.23	43.2	24.0	4.7
L.M.	−	13.2	28.0	2.12	69.2	37.0	16.5
R.McD.	+	22.8	76.2	3.33	175.7	98.5	53.5
M.H.	−	22.1	67.2	3.04	154.4	86.8	55.9
M.K.	−	27.0	68.0	2.51	163.0	92.0	45.7

IMP—inosinic acid
ADP—adenosine diphosphate
ATP—adenosine triphosphate
P—phosphate
CP—creatine phosphate

given in table 3. Histologic slides were studied without knowledge of the clinical picture and were described in accordance with a recent atlas on the subject.[14] Note that, in the majority of instances, the histologic picture was consistent with that seen in familial progressive muscular dystrophy. In one case the histologic appearance was within normal limits and in two cases the histology was more suggestive of neurogenic disease, despite clinical pictures quite in keeping with a diagnosis of progressive muscular dystrophy. The degree and type of mononuclear cell collections (inflammatory foci) seen in a few of the cases were all within limits of those seen in familial muscular dystrophy.[14]

The creatine and creatinine excretion is also recorded in table 3. The sum of the two values is equal to the creatinine excretion in normal individuals of similar age and weight, indicating a normal synthesis of creatine. The percentage of the total excreted as creatine is variable, but in all cases except three of the women investigated it amounted to over 50 per cent of the total. The amount excreted seemed to correlate fairly well with the physical disability of the patient.

As might be expected from the known variability in the way in which individual muscles are affected by this disease, no direct correlation can be drawn between the creatine excretion and the decreased creatine content at the muscle analyzed. The earlier biopsies were taken from more seriously affected muscles. In these muscles the creatine phosphate and total creatine of the muscle were very low.

It was thought that, since this is a genetically transmitted disease and if the primary

TABLE 3

HISTOLOGIC FINDINGS, GENERAL FUNCTIONAL DISABILITY, CREATINE EXCRETION, AND TOTAL CREATINE + CREATININE EXCRETION IN PATIENTS STUDIED

Patient	Sex	Age	F.H.	Histologic Findings			Functional Disability	Excreted 24 hr.	
				Principal Lesion*	Fat	Collagen	Inflammatory Foci		Creatine + Creatinine	Creatine
									mg.	mg.
T.C.	M	8	+	W	0	0	0	++	865	419
L.R.	M	16	+	N	0	0	rare	++	1460	735
L.J.	M	14	–	–	–	–	–	++	–	–
H.G.	F	57	+	M	+	+	0	+	970	220
G.F.	F	34	+	M	+	0	0	+	1040	196
J.McD.	M	10	–	M	+++	0	0	+++	1390	846
J.F.	M	45	+	M	±	0	0	++	1650	760
B.F.	M	21	+	M	+	0	mild	+++	1160	873
R.A.	M	51	+	–	–	–	–	+++	935	628
L.Re.	M	11	+	M	+++	0	rare	+++	585	396
J.Re.	M	10	+	M	+++	0	0	+++	615	414
L.W.	M	12	+	M	+++	0	0	+++	1190	791
L.M.	F	38	?	M	+++	0	0	+	1530	491
M.H.	M	10	–	M	+	0	mild	++	680	394
M.K.	F	26	–	M	+	0	rare	+	1340	556
R.McD.	M	18	+	N	0	+		+	–	–
Myotonic dystrophy										
W.D.	M	30	–		0	0	rare		1755	15

*Principal lesion: N = neurogenic, M = myogenic (myopathic, non-neurogenic), W = within normal limits.
– No observations.

lesion is in the muscle, it must exist in all muscles, and the peculiar distribution and extension of the disease must somehow be related to the function of the muscle. If the lesion is biochemical in nature, it would be more easily discovered in less atrophied muscles. When analyses were extended to the more normal muscles, it was found that, while the creatine phosphate and creatine were still well below normal, they were considerably higher than in the more seriously affected muscles and the nucleotides in many cases were hardly reduced below the normal value. This was true even though the muscle selected was from a seriously disabled patient. In the case of patient R.A., for example, the only superficial muscle that appeared to be functionally satisfactory was the brachioradialis. Myographic records taken on the day before the biopsy showed normal records and well sustained contractions. On analysis, this muscle appeared to be in fairly good condition, with 49 per cent of the normal creatine phosphate value and 86 per cent of the normal high energy phosphate in the form of nucleotides. Patient R.L., while seriously affected with a marked lordosis and weakness of shoulder muscles, was capable of walking and moving about. The trapezius muscle, in which the functional involvement was serious, showed a reduction of the creatine phosphate to 27 per cent of the normal and of the nucleotide high energy phosphate to 43 per cent of normal. The three female patients investigated present an interesting picture. They were all rather obese but were all carrying on relatively normal activities, although complaining of weakness. In all three the fat content of the muscle was high, leaving the protein content low. Although on a weight basis the values for creatine phosphate and nucleotides were low, when calculated to a noncollagen protein basis the values for H.G. and G.H. showed creatine phosphate of 54 and 78 per cent of the normal, while the third showed only 16 per cent. The nucleotides were 69 and 90 per cent of the normal value in the first two and 24 per cent in the third case. Although all of these women were excreting creatine and the third more than the other two, they were all converting from two-thirds to three-fourths of the total to creatinine.

In all of the dystrophic muscles investigated, the creatine phosphate and total crea-

tine content of the muscle was low. Even in the case of R.MCD., which appeared to be quite normal in function and pathology except for slight increase in collagen, showed the creatine phosphate to be only one-half of the normal amount. The energy rich phosphate as nucleotide in this muscle was within normal limits. In other muscles of this series the high energy nucleotides were always maintained better than creatine phosphate.

It should be kept in mind that, in these comparisons, the normal values were obtained on muscles anatomically different from those of the patients. Two different anatomic groups of muscles were used in the normals and these contain about the same concentrations of these phosphate compounds. A more extensive analysis of different muscles is contemplated as they can be procured from relatively normal individuals at operations. From our work on rats, in which a number of different muscle groups have been studied, the chief difference appears to be in the amount of collagen in the muscle. When the concentrations of high energy phosphate are referred to the noncollagen protein, the differences between different muscles are slight and of the same order as the differences observed in the same muscles from different individuals. At the present time it is not felt that the failure to use the same muscle for control value influences the interpretation of these results.

SUMMARY

A comparison has been made between the biopsy muscle of normal humans and dystrophy patients with respect to energy rich phosphate compounds.

On a noncollagen protein basis, the creatine phosphate and the total creatine of the dystrophic muscles was lower than in normal muscle. The creatine phosphate content varied from 4 to 56 per cent of normal value, except in one muscle which contained 78 per cent of the normal amount.

The ratio of creatine phosphate to creatine was the same as for normal muscle. The high energy nucleotide phosphate was better maintained than the creatine phosphate. In about 50 per cent of the dystrophic muscles, the value amounted to 70 per cent or more of that found in normal muscle. The lowest value found was 24 per cent of normal.

The low creatine phosphate and creatine content of dystrophic muscles is consistent with the finding of low creatinine and high creatine excretion assuming a normal synthesis of creatine.

The failure to retain creatine is not due to the lack of adenosine triphosphate necessary for its synthesis.

The technical assistance of Donagene Thurmond is acknowledged. We greatly appreciate the cooperation of the following doctors who provided patients for these studies: Dr. Irwin Levy, Dr. William M. Landau, and Dr. Charles Carter. Dr. Arthur Stein procured the biopsy material on normal and some of the dystrophy patients.

REFERENCES

1. Block, K., and Schoenheimer, R.: The biological precursors of creatine. J. Biol. Chem. 138:167, 1941.
2. Borsook, H., and Dubnoff, J. W.: The hydrolysis of phospho-creatine and origin of urinary creatinine. J. Biol. Chem. 168:493, 1947.
3. Benediot, J. D., Kalinsky, H. J., Scarrone, L. A., Werthein, A. R. and Stetten, D. Jr.: The origin of urinary creatine in progressive muscular dystrophy. J. Clin. Investigation. 34:141, 1956.
4. Hoagland, C. L., Gilder, H., and Shank, R. E.: The synthesis, storage and excretion of creatine, creatinine, and glycocyamine and effect of certain hormones on these processes. J. Exper. Med. 81:423, 1945.
5. Fiske, C. H., and Subbarow, Y.: The colorimetric determination of phosphate. J. Biol. Chem. 66:375, 1925.
6. Furchgott, R. F., and de Gubareff, T.: The determination of inorganic phosphate and creatine phosphate in tissue extracts. J. Biol. Chem. 223:379, 1956.
7. Lowry, O. H., Roberts, N. R., Leiner, K. Y., Wu, M., and Farr, A. L.: The quantitative histochemistry of brain. I. Chemical methods. J. Biol. Chem. 207:1, 1954.
8. Borsook, H., and Dubnoff, J. W.: The formation of creatine from glycocyamine in the liver. J. Biol. Chem. 132:559, 1940.
9. Neuman, R. E., and Logan, M. A.: The determination of hydroxy-proline. J. Biol. Chem. 184:299, 1950.
10. Cohn, W. E., and Carter, E. C.: Separation of adenosine phosphates by ion-exchange and paper chromatography. J. Am. Chem. Soc. 72:4273, 1950.
11. Jordan, W. J., and Gray, I.: Biochemical response to trauma. I. Nucleotide changes in tourniquet shock. J. Biol. Chem. 251:669, 1955.
12. Fischer, E., and Ramsey, V. W.: Changes in protein content and in some physico-chemical properties of the protein in muscular atrophy of various types. Am. J. Physiol. 145:371, 1946.
13. Fischer, E.: Changes in protein and enzymes in muscular degeneration subsequent to denervation. Proceedings of 3rd Medical Conference of the Muscular Dystrophy Association of America, Inc. pp. 212-223, 1954.
14. Greenfield, J. G., Shy, G. M., Alvord, E. A., Berg, L.: Atlas of Pathology in Neuromuscular Diseases. E. & S. Livingstone, Ltd., Edinburgh, 1957.

Neurologic implications of Behcet's syndrome

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In 1937 Behcet,[1] a Turkish dermatologist, described five cases of recurrent ulceration of the mouth and genitals with recurrent uveitis, and reported finding inclusion bodies in scrapings from the ulcers and in the hypopyon fluid in some cases. He regarded this as evidence of a specific virus responsible for the syndrome, and so entitled his paper "Ueber rezidivierende Aphthöse durch ein virus verursachte Geschwüre am Mund, am Auge und an den Genitalien." Sporadic cases of a similar nature had been reported previously. For instance, in 1923 Chauffard[2] and his colleagues had given details of a case of what must now be regarded as Behcet's syndrome, which had also shown an episode of encephalitic symptoms. However, such cases had not been recognized as a specific disease entity nor had a definite etiology been suggested previously.

A typical case of the syndrome may occur in young adult life, with herpetic vesicles in the mouth which rapidly break down to sloughing ulcers and heal slowly with some scarring. In three to six months' time similar lesions may appear on the genitals, and in a further few months the first attack of iritis may occur. The episodes, accompanied by a mild constitutional upset, tend to recur two or three times a year, though intervals may be much longer. Cases have been recorded with a relatively benign course, with continuing recurrences up to 20 years. Pain is often a prominent feature of the ulceration. If the eye is affected, it may give rise to severe radiating headache which may be so severe as to call for enucleation of the eye, if it is already severely damaged. The initial attack may be in any one of the three sites. Following Curth's[3] suggestion, it is now usual to accept the clinical diagnosis if any two of these symptoms occur in a given case.

Since Behcet's original description, other features have been added. Though less constant, they are of diagnostic value. Recurrent erythema nodosum,[4] episodes of thrombophlebitis – even to the extent of complete occlusion of the inferior vena cava in one case,[5] and transient arthropathies usually with effusion,[3] occur in over half the reported cases. Involvement of the central nervous system has been noted in a much smaller number of cases. It is this which makes the condition more than just another recurrent exudative syndrome, such as Reiter's or Stevens-Johnson disease.

Apart from more deep seated neurologic involvement, the uveitis in some cases of what may be called classical Behcet's syndrome illustrates some invasion of the nervous system proper. Although recurrent iridocyclitis, usually with hypopyon, is the most common form that the uveitis takes, retinitis, choroidoretinitis, and retrobulbar neuritis with characteristic scotoma have been recorded in earlier cases.

Clinical signs of undoubted central involvement have been reported in only 17 cases so far. It is fortunate that such involvement is uncommon, because it seems to carry a very bad prognosis. The mucocutaneous and eye lesions, though they may cause painful scarring and substantial loss of vision, seem to have no direct mortality. Of the 17 reported neurologic cases, however, seven died.

Two useful reviews of such cases have appeared recently. Pallis and Fudge[7] reviewed the literature and reported two cases of their own, and Wadia and Williams[8] added three further cases.

The main features of the neurologic involvement are the relapsing nature, with periods of remission, improvement, and even complete disappearance of signs between episodes; the predilection for a brainstem localization; and the tendency for motor signs to be far more common than sensory. Episodes may suggest recurrent or spreading involvement of the same site, or they may indicate entirely new locations of lesions. They are usually but

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not always accompanied by fresh outbreaks of ulceration. Headaches are a constant feature and signs of transient meningeal involvement are common. The cerebrospinal fluid usually shows a lymphocytic pleocytosis with elevated protein, though cases are recorded with a normal fluid at the time of an acute episode. In the deaths so far reported, this has occurred within three years of the initial neurologic episode in all cases. Autopsy findings will be discussed later when etiology is considered. All cases presented between the ages of 16 and 45, the majority being under age 30. Of a total of 19 cases, including the two reported here, 12 were male and seven female.

CASE REPORTS

Two cases of the condition have been seen in this department in the past 18 months. In the first the diagnosis is reasonably certain; in the second it is clinically probable but still in doubt.

Case 1. A woman aged 31 with six years' of recurrent joint effusions, two years' recurrent ulcers of the mouth and vulva, 18 months' uniocular scotoma, and 12 months' recurrent right hemiparesis and brainstem signs

This patient was referred to a rheumatism clinic in September 1956 because for five years, shortly after the birth of her second child, she had had recurrent hydrarthrosis of one or both knees and ankles. This had usually, though not always, occurred at the times of her menstrual periods. During her third and last pregnancy three years previously, this symptom had been in abeyance. There was a past history of an erythema nodosum rash at the age of 19 which lasted for 14 months. There was no history of tuberculosis. Since June 1955 she had had recurrent ulceration of the mouth and vulva, occurring in bouts every three to four months. In November 1955 she had developed blurred vision in the left eye which cleared in about six weeks, but left a small blind spot of which she was subjectively aware.

Some two weeks before admission she had suddenly developed right hemiparesis with slight aphasia. This resolved almost completely in five days. Three days later, however, it recurred, with drowsiness, headaches, and neck stiffness. Two days later a further episode occurred, with vomiting, diplopia, and slurred speech, in addition to the dysphasia. Since her referral in September she had been on cortisone 75 mg. a day for ten days and then 50 mg. a day, and she was still on this dosage when neurologic signs developed.

When transferred to the neurology department 15 days after the onset of these signs, she was alert but euphoric. There was obvious flaccid right hemiparesis involving the face, arm, and leg, with minimal dysphasia but no convincing sensory loss. There was dysarthria and ataxia of gait and limbs, with nystagmus and limitation of upward gaze. The left optic fundus showed a pale disk with some tiny, scattered patches of choroiditis and small peripheral hemorrhages. The right fundus was normal. Visual field charts revealed a small left eye scotoma, controcecal at about the four o'clock position. On general examination there was a small effusion in the left knee joint and old ulcer scars on the labia, with recent healed ulcers in the mouth.

The cerebrospinal fluid showed 25 lymphocytes per cu. mm. and 35 mg. protein per 100 ml. A left carotid angiogram was normal. Blood count showed a neutrophil leukocytosis of 80 per cent in a total of 20,600 white cells. Plasma proteins were normal. Wassermann reaction was negative in blood and fluid.

A diagnosis of Behcet's syndrome was accepted. The corticoid dosage was increased to 60 mg. of Prednisone a day for 18 days. During this time her mental state became rather manic, but hemiparesis and brainstem signs cleared steadily. Five days after starting Prednisone she developed a fresh crop of ulcers in the mouth. She was sent home with a residual hemiparesis but no ataxia or nystagmus. For the next four months she was given a maintenance dose of 10 mg. of Prednisone daily and during this time she had an attack of diplopia which lasted ten days. When seen one year after her initial neurologic episode, she still had some spastic right hemiparesis though she could walk and do her housework. Her speech was slurred but there was no other brainstem sign. The optic fundi were normal, except for some pallor of the left disk. There was some urgency but rarely incontinence of urine. Her emotional state was abnormally labile. She had had no further ulcers since December 1956.

Neutralizing antibodies to a virus isolated from a case of Behcet's syndrome were present in her serum to a titer of 1:64.

Clinically, this case showed the triad of Behcet's syndrome. Neurologic involvement, which had been present for 14 months, had shown at least three separate episodes relating to cortical and brainstem sites. Incomplete remission of symptoms had occurred between episodes. The clinical diagnosis here was confirmed by the presence of virus neutralizing antibodies.

Case 2. A man aged 44 with three years' recurrent ulceration of the mouth, two years' variable scotomatous defect of both eyes. 18 months' fluctuating spastic paraparesis with brainstem signs, and six months' ulceration of the left cornea.

This man was seen in February 1956 because of four months' fluctuating impairment of vision

affecting the right eye more than the left. On direct questioning he gave a two year history of recurrent ulceration in the mouth. Ulcers occurred in bouts every three to four months. On examination at this time he had bilateral incongruous scotomata. The right disk was abnormally pale, but the fundi were otherwise normal. There was fine lateral nystagmus but no other convincing abnormalities in the central nervous system. During the next three months he developed a spastic weakness of the left leg, but the scotomata cleared in the left eye and receded in the right. When seen in July 1956 his left leg had improved greatly. There was no clinical spasticity, though the plantar response was still equivocal. A month later he gradually developed slight bilateral spastic paraparesis with urgency of micturition. This cleared in four months, but unsteadiness of gait developed. On examination in June 1957 he showed ataxia of gait and of all four limbs, with nystagmus but no dysarthria. There were no sensory signs. This condition improved but is still present. Recurrent ulceration of the mouth has continued and in April 1957 he had his first episode of corneal ulceration. Since then one further attack has occurred.

It was not possible to examine for virus neutralizing antibodies in this case.

Clinically, this case was first considered to be multiple sclerosis, and it is still possible that this may be the correct diagnosis. However, the recurrent oral ulceration and uveitis, two of the symptomatic triad of Behcet's syndrome, make this latter a probable diagnosis.

Case 2 illustrates well the difficulty of purely clinical diagnosis. As might be expected the differentiation from multiple sclerosis which is presented here has already proved a stumbling block. One case of Phillips and Scott[9] had been diagnosed as multiple sclerosis, and Knapp's[10] case also suggested this until a characteristic uveitis developed.

DISCUSSION

The etiology of a disease such as this, which can produce recurrent episodes of neurologic disability, is of some importance and the neurologic implications of the syndrome really derive largely from our views on its etiology.

Behcet's initial claims to have found inclusion bodies in his cases were not confirmed at first and the virus origin remained in doubt. Some support for his view came from Alm and Oberg[11] who claimed to have produced uveitis in rabbits by intracisternal injection of cerebrospinal fluid from patients with Behcet's syndrome. Sezer[12] also claimed to have isolated a virus from the vitreous and subretinal effusion of a patient, grown it successfully on chorionic membrane, reproduced encephalitis by intracerebral inoculation in mice, and further obtained complement fixation and neutralizing antibody reactions with sera from cases of Behcet's syndrome. These results remained unconfirmed. His later claims[13] to have isolated virus from blood and urine of patients during the active ulceration phase were viewed with scepticism, because his uniformly positive cultures on chorionic membrane seemed too good to be true. However, recently Evans, Pallis, and Spillane[14] reported successful culture of a virus from the aqueous and from the brain tissue and cerebrospinal fluid of a fatal case of the disease. His claims—a positive growth of three out of 30 inoculations—sounded more in keeping with the usual behavior of such cultures. Having established the strain by passage, Evans used these cultures for virus neutralizing antibody estimations and showed that such antibodies were present in significant titers in 11 cases of clinical Behcet's syndrome, including case 1 of this paper. They were not present in 14 control sera nor in one case of Reiter's syndrome.[15] These results seem to confirm the clinical impression of a virus infection, and their repetition in other laboratories will be looked for with considerable interest.

Proved virus infections of the nervous system have so far been known to produce usually only a single acute episode, often severe and with a high mortality, as in St. Louis or Japanese B. encephalitis, equine polioencephalomyelits, or herpes simplex encephalitis. In von Economo's encephalitis there is some clinical and histologic evidence for recurrent episodes, but these are not sharply defined and its virus etiology, although probable, remains unproved. Multiple sclerosis is the outstanding example of a disease showing recurrent neurologic episodes. The difficulties of clinical differentiation between this and Behcet's syndrome have already been mentioned. The cause of multiple sclerosis remains unknown, but Russian claims to have isolated a virus take on a fresh interest, in view of Evans' work. If his findings are accepted, then we see in Behcet's syndrome the first proved example of a virus infection causing recurrent involvement of the central nervous system. However, the absence of confirmed inclusion bodies and the negative re-

sults of Evans' animal inoculations still provide grounds for doubt.

Apart from the etiology of the disease, there remains the interesting question of the exact mode of production of these recurrent neurologic symptoms. The possibiility that they represented recurrent thrombotic episodes was considered at one time, because of the known phlebothrombotic attacks in the disease and because of seemingly primary thrombosis of venules and arterioles around the skin lesions. The histologic picture in the brain does not exclude this entirely, but there is in general a striking absence of unequivocal evidence of primary thromboses in autopsy material. If this can be dismissed, two other possibilities must be considered. Do the symptoms and signs that occur represent actual recurrent virus infection of the central nervous system, or may they be simply sensitization phenomena to the recurrent allergen of general bodily virus infection? Recurrent direct infection would only occur if immunity was short lived, and Sezer[13] claimed to have shown that antibody titers are only raised for a few months following acute ulcerative episodes. This is certainly in keeping with the time pattern of ulcer formation. Direct evidence on this point is lacking, as no inclusion bodies have been reliably described and successful cultures have been made only with material which included brain and other tissue and never from brain alone. Indirect evidence may come from two sources: 1) the response to corticoids, which can be expected to suppress or modify sensitization reactions if used in adequate dosage, and 2) from the histology of the brain lesions, since a sensitization encephalopathy has histologic features which may distinguish it from a primary inflammatory reaction.

So far as corticoids are concerned, the evidence is conflicting. Phillips and Scott[9] claimed striking improvement with cortisone in four cases, though the skin lesions responded better than the nervous system. Wadia and Williams[8] were also impressed with its effects in one case. Our first case was largely unaffected by cortisone, though the dosage was large. In general, temporary control of ulceration may be achieved but the time relations of remission of neurologic signs do not suggest a causative effect. However, it may be that the dosage used is too small, because in polyneuritis and known allergic encephalitis the effective dosage may have to be 300 to 500 mg. of cortisone a day, and no results from dosages of this size in Behcet's syndrome have as yet been published. Present results certainly give no positive support to an allergic mechanism for the neurologic involvement.

The histologic evidence is also unsatisfactory. Of the seven recorded deaths, post mortems were obtained in five. In one of these the diagnosis was not beyond doubt[16] and in two others the histologic details were inadequate.[17,18] Two cases have been recorded with detailed histology by McMenemey and Lawrence.[19] They summarized their findings as focal softening in relation to blood vessels, perivascular lymphocytic infiltration with slight associated loss of myelin, and some vascular cuffing in white matter. This picture suggested a series of episodes of local vascular insufficiency, with no evidence of active thrombosis. They pointed out that the picture differs markedly from that of multiple sclerosis in the absence of any widespread demyelinization with preserved axons, in the lack of any intense glial overgrowth, and also in the distribution of lesions which is not that of the characteristic multiple sclerosis pattern. The misleading clinical similarity between the two is thus clearly unmasked histologically. In general, the histologic findings in Behcet's syndrome are similar to some cases of herpes simplex encephalitis, which is a result of direct cerebral invasion of the virus, and to cases of encephalitis following secondary vaccination, which is largely a sensitization effect.

Thus far neither response to corticoids nor histologic findings help in clarifying the mechanism of brain involvement. The important neurologic implication is that we are probably seeing for the first time a definite example of virus infection producing, by one method or the other, recurrent and to some extent remitting signs in the central nervous system. However, the unsolved problem of the mechanism of neurologic involvement is likely to contain more of interest to the study of the nervous system than the simple fact of virus infection.

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REFERENCES

1. Behcet, H.: Ueber die rezidivierende Aphthöse durch ein virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. Dermat. Wchnschr. 105:1152, 1937.
2. Chauffard, A., Brodin, P., and Wolf, M.: Stomatite et vulvite aphteuses, suivies de troubles dementiels passager. Bull. et mém. Soc. méd. hôp. Paris 47:841, 1923.
3. Curth, H. O.: Recurrent genito-oral aphthosis and uveitis with hypopyon. Arch. Dermat. & Syph. 54: 179, 1946.
4. France, R., Buchanan, R. N., Wilson, M. W., and Sheldon, M. B.: Relapsing iritis with recurrent ulcers of the mouth and genitalia. Medicine 30:335, 1951.
5. Thomas, E. W. P.: So-called triple-symptom complex of Behcet. Brit. M. J. 1:14, 1947.
6. Gray, G. S.: The triple complex syndrome of Behcet. Canad. M.A.J. 62:597, 1950.
7. Pallis, C. A., and Fudge, B. J.: The neurological complications of Behcet's syndrome. Arch. Neurol. & Psychiat. 75:1, 1956.
8. Wadia, N., and Williams, E.: Behcet's syndrome with neurological complications. Brain 80:59, 1957.
9. Phillips, D. L., and Scott, J. S.: Recurrent genital and oral ulceration with associated eye lesions. Lancet 1:366, 1955.
10. Knapp, P.: Beitrag zur Symptomatologie und Therapie der rezidivierenden Hypopyoniritis und der begleitenden aphthösen Schleimhauterkrankungen. Schweiz. med. Wchnschr. 71:1288, 1941.
11. Alm, L., and Oberg, L.: Animal experiment in connection with Behcet's syndrome. Nord. med. 25:603, 1945.
12. Sezer, N.: The isolation of a virus as the cause of Behcet's disease. Am. J. Ophth. 36:301, 1953.
13. Sezer, N.: Further investigations on the virus of Behcet's disease. Am. J. Ophth. 41:41, 1956.
14. Evans, A. D., Pallis, C. A., and Spillane, J. D.: Involvement of the nervous system in Behcet's syndrome. Lancet 2:349, 1957.
15. Evans, A. D.: Personal communication, 1957.
16. Silfverskiold, B. P.: Recurrent uveitis (Behcet's syndrome) with encephalomyelomeningitis. Acta psychiat. et neurol. 26:443, 1951.
17. Berlin, C.: Behcet's syndrome with involvement of the nervous system. Arch. Dermat. & Syph. 49:227, 1944.
18. Magni, S.: Morbo di Behcet con manifestazioni meningoencefalitiche. Riv. oto-neuro-oftal. 26:445, 1951.
19. McMenemey, W. H., and Lawrence, B. J.: Encephalomyelopathy in Behcet's disease. Lancet 2:353, 1957.

■ Spencer says: "The difference between an involuntary movement of the leg and a voluntary one is that, whereas the involuntary one takes place without any previous consciousness of the movement to be made, the voluntary one takes place only *after it has been represented in consciousness.*" The voluntary is preceded by a nascent excitation of the parts to be moved. In the next communication I hope to show that in active physical processes, motor and sensory, there is subjective reproduction prior to objective reproduction — a sensation, for instance, is first put in relation to its subject, and next considered in relation to its subject — that there is something like a reduction of relations of sequence to relations of co-existence (i. e. of alternate sequence) in the two terms of a proposition; and that what I have advanced as to the crossed differences of the two brains is in harmony with this view as regards both the related pairs, voluntary and involuntary perception, and voluntary and involuntary expression.

J. Hughlings Jackson in *Notes on the Physiology and Pathology of the Nervous System,* published in 1868.

Cerebrospinal fluid free amino acids in neurologic diseases

Observations in aspartic acid concentrations

John Logothetis, M.D.

DURING THE COURSE of a survey study of the cerebrospinal fluid free amino acids, it was noted that two patients with hereditary cerebellar ataxia exhibited high amounts of free aspartic acid in the cerebrospinal fluid. A similar observation was made by Kemali and was included in his clinical study of hereditary spinocerebellar ataxia.[1] Kemali utilized paper chromatographic analysis to separate the cerebrospinal fluid free amino acids in four cases with this disease. In his studies of normal cerebrospinal fluid using 0.6 ml. samples, he could not detect free aspartic acid, but he consistently found the latter in all four cases of ataxia examined. No quantitation was carried out.

MATERIALS AND METHODS

The observations of cerebrospinal fluid free amino acids in this report were made in two brothers who were both afflicted by hereditary cerebellar ataxia. The spinal fluid was removed by a lumbar puncture and kept under deep refrigeration until processed. The protein, sugar, cells, and Wassermann reactions were negative in both cases. Separation of the free amino acids was carried out by two-dimensional paper chromatography, using saturated phenol in water and lutindine-ethanol-water mixture in proportions 10:5:5, respectively. The quantitative procedure involved direct photometry (maximum color density) and the usage of prepared calibration curves. Details of our method were presented elsewhere.[2]

RESULTS

The chromatographic analysis of cerebrospinal fluid of these two cases showed that, among 15 free amino acids separated, aspartic acid was significantly increased over the normal range. In addition, other amino acids, particularly alanine, serine, glycine, lysine, and threonine, appeared moderately elevated. The normal base line was obtained from the study of 52 individuals who were free of neurologic disorder, systemic disease, or psychosis.[3] The normal free aspartic acid, as determined with our method, ranges between 0.3 to 2.2 micrograms per ml., with a mean of 1.1. The first case with ataxia exhibited 2.7 micrograms per ml. of free aspartic acid, and the second exceeded this amount. The latter could not be determined accurately, since the method used does not permit accurate estimation over a concentration of 2.7 micrograms per ml. The above described changes in aspartic acid were statistically significant. Changes in the other five amino acids mentioned above were not as striking; however, all appeared in the extreme upper normal ranges. Figure 1 presents the chromatograms in these two cases with hereditary cerebellar ataxia, along with a normal chromatogram for comparison.

Some 200 cerebrospinal fluid samples were examined from patients with other degenerative, vascular, neoplastic, toxic, and traumatic disorders of the nervous system, but in none was such a change in the aspartic acid detected.

DISCUSSION

The results of this study indicate possible biochemical alterations related to the central

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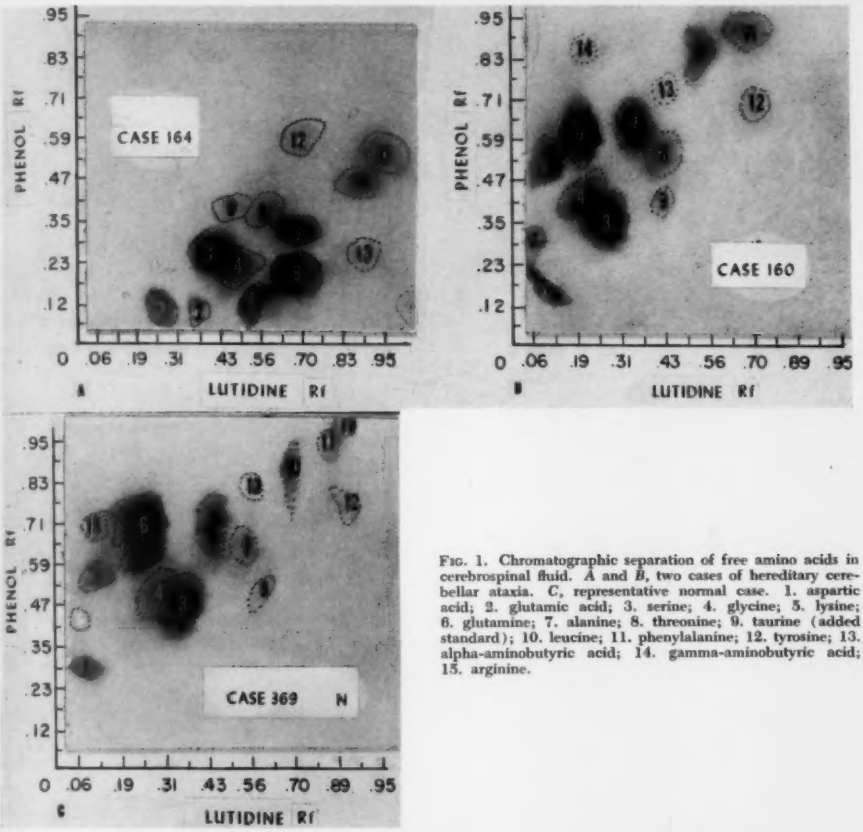

FIG. 1. Chromatographic separation of free amino acids in cerebrospinal fluid. *A* and *B*, two cases of hereditary cerebellar ataxia. *C*, representative normal case. 1. aspartic acid; 2. glutamic acid; 3. serine; 4. glycine; 5. lysine; 6. glutamine; 7. alanine; 8. threonine; 9. taurine (added standard); 10. leucine; 11. phenylalanine; 12. tyrosine; 13. alpha-aminobutyric acid; 14. gamma-aminobutyric acid; 15. arginine.

nervous system in two cases of cerebellar ataxia. Such alterations may be a characteristic phenomenon in this disorder or perhaps a biochemical change common to more than one clinicopathologic entity. The latter is possible since some increase of aspartic acid was found in Parkinson's disease.[4] Moreover, marked increases in free aspartic acid were observed in brain extracts of rats rendered hypoglycemic by insulin before sacrifice.[5] In the latter study the increase in aspartic acid was associated with decreases in glutamic acid, gamma-aminobutyric acid, and glutamine, with no change in free aminonitrogen. The authors suggest that such alterations most likely reflect activation of glutamic-oxaloacetic transamination reaction so that, from the products formed, the alpha-ketoglutaric acid may be used for energy production.

It is possible that the increases observed in the cerebrospinal fluid free amino acid of the two cases of cerebellar ataxia may also reflect an activation of transamination reactions, particularly between glutamic-oxaloacetic acids, to yield aspartic acid. This transamination reaction is known to be one of the most rapid reactions brought about by the brain.[6] Among other tissues only muscle is more active than the brain in this respect. In connection with our observations in ataxia, it is interesting that the cerebellar tissue of dogs was found to have the highest transaminase activity, exceeding by

two or three times that of the medulla, white matter, and cerebral cortex.[7] Increased transaminase activity in the cerebrospinal fluid was observed in cases of acute cerebral necrosis.[7,8] Such a phenomenon has not been described in degenerative neurologic disorders. A limited number of such cases including amyotrophic lateral sclerosis and senile dementia were examined, but did not show any increase in transaminase activity in the cerebrospinal fluid.[8]

SUMMARY

1. The study of free cerebrospinal fluid free amino acids in two cases of hereditary cerebellar ataxia revealed significant increased amounts of aspartic acid and, to a lesser extent, of other amino acids.

2. The above observation correlates well with a previous observation made regarding increase in aspartic acid in some cases of hereditary spinocerebellar ataxia.

REFERENCES

1. Kemali, D.: Sulle eredo-degenerarzioni spino-cerebellari e sulle relative forme di associazone. Acta Neurol. Napoli 9:358, 1954.
2. Logothetis, J.: A study of free amino acids in the human cerebrospinal fluid. Neurology 5:767, 1955.
3. Logothetis, J.: The free amino acid content of cerebrospinal fluid in humans and dogs. Neurology 8:299, 1958.
4. Torre, M., Scarzella, R., and Zanalda, A.: Gli aminoacidi liberi del sangue e del liquor in malati di morbo di Parkinson. Minerva med. 2:256, 1953.
5. Grarioto, R. D., Massieu, G., and Izquierdo, J. J.: Free amino acids in rat brain during insulin shock. Proc. Soc. Exper. Biol. & Med. 78:856, 1951.
6. Cohen, P. P., and Hekhuis, G. L.: Rate of transamination in normal tissues. J. Biol. Chem. 140:711, 1941.
7. Wakim, K. G., and Eleisher, G. A.: The effect of experimental infarction on transaminase activity in serum, cerebrospinal fluid, and infarcted tissue. Proc. Staff Meet., Mayo Clin. 31:391, 1956.
8. Green, J. B., et al.: Cerebrospinal fluid glutamic oxaloacetic transaminase activity in neurologic disease. Neurology 7:313, 1957.

■ I think there is evidence that in some parts of the cerebellum there is a unilateral representation in the order from trunk movements to movements of the hands and feet. I have no doubt that Brown-Séquard is right in saying that tumour pressing on the crus cerebelli produces paralysis of the same side, and I believe this is mainly of movements of the trunk and those passing to the upper parts of the limbs. The erratic movements of the arms in some of these cases partly depend, I think, on paresis of muscles attaching the limb to the trunk.

There are indirect symptoms from tumour of the middle lobe and large tumours under the tentorium. There is vast increase of fluid in the lateral ventricles of the cerebrum in some cases. In children the head enlarges; thre is great hebetude of mind, a slow failure of mental faculties.

J. Hughlings Jackson in *On Tumours of the Cerebellum*, published in 1881.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by D. Frank Benson, M.D., Knox Finley, M.D. and California S. Ushiro, M.D.

CASE PRESENTATION

A 29 year old white farmer was admitted to the diagnostic center of the Veterans Administration Hospital in San Francisco in February 1949 and transferred to the neurosurgical service in March 1949. He had been perfectly well until August 1946, when he had the onset of episodes consisting of blurred vision, screaming, and loss of consciousness. There is also a history of difficulty with speech and reading at this time. In December 1946 he was admitted to the Portland Veterans Administration Hospital where an extensive workup was performed. In January 1947 a left parietal craniotomy was performed. No evidence of a pathologic process was found at surgery, but it was felt that neoplasm was the most likely diagnosis. Postoperatively the patient noted a right hemiparesis and speech difficulty which cleared slowly. Also postoperatively the patient noted a hemianopsia which had not been present prior to surgery. During the subsequent two years, the patient had a number of epileptic attacks involving the right side. In 1947 he was again seen at the Portland Veterans Administration Hospital, where the diagnosis was changed to diffuse cortical atrophy of the brain with right hemiparesis. One epileptic attack occurring after hospitalization in February 1949 involved both sides. The patient stated his left side became numb and he did not know where it was.

Past history revealed that the patient served in the Army in the South Pacific and in the Philippines on the Island of Leyte. He was never ill or injured and did not require hospitalization.

General physical examination revealed a young male patient in no acute distress, who was somewhat dulled mentally but quite cooperative. Blood pressure was 100/60, pulse 60. The remainder of the general examination was not remarkable.

Neurologic examination revealed a left homonomous hemianopsia involving the entire lower quadrant and part of the upper quadrant. The optic disks were normal except for some pallor. Both touch and pinprick were discerned better on the right side of the face than the left, and the right corneal reflex was more active than the left. A right facial weakness was present and there was possibly a mild weakness of the right arm and leg. The deep reflexes were hyperactive throughout. There were bilateral positive Hoffmann's signs, the left abdominal reflex was absent, but there were no other abnormal reflexes. There were no cerebellar signs. Sensation was intact, except for astereognosis of the right hand and loss of two-point discrimination over the right extremities.

Laboratory data. Red blood count 4.91 million; hemoglobin 14 gm.; white cell count 5,800, with a normal differential; sedimentation rate 5. Urinalysis was negative. Feces negative for blood, ova, and parasites. Basal metabolism was minus 14. A skull film showed an old craniotomy of the left frontoparietal region. Roentgenograms of the lumbar spine were negative. Lumbar puncture showed normal dynamics and the spinal fluid was clear, contained two lymphocytes, negative globulin, protein 17 mg. per cent, and negative serology. A repeat spinal fluid showed no cells, sugar 65 mg. per cent, faint trace of globulin, and a total protein of 38 mg. per cent. An electrocardiogram was negative. An electroencephalogram on February 3, 1949 was abnormal, with focal slow waves on the left, most marked in the occipital and temporal regions. A pneumoencephalogram on February 21, 1949 showed the left lateral ventricle to be markedly dilated, while the right ventricle was nearly normal in size. There was a shift of the midline structures to the left. The dorsal portion of the right lateral ventricle was indented on its superior surface by a right parietal mass. A right carotid angiogram indicated a negative area in the parietal region. No angiomatous vessels were noted.

On March 10, 1949 the patient was operated upon again and a right temporal bone flap was turned. When the cortex was exposed, it was noted that it pulsated somewhat less than usual, the gyri were small, and the cortex in the inferior parietal region had a curiously fine vascularity. This area was much firmer to palpation than normal. Probing revealed a firm mass just below the surface of the parietotemporal cortex, and a biopsy was made. A sizeable subdural decompression was then carried out and the incision closed. The patient made an uneventful postoperative recovery and on the eighteenth postoperative day was started on specific therapy. On the twenty-fifth postoperative day the patient suddenly developed sharp pleuritic pain and hemoptysis. This persisted

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and he became febrile. On the thirtieth postoperative day the patient sat up in bed, complained of severe upper abdominal pain, became cyanotic, went into shock, and expired.

DISCUSSION

DR. C. S. USHIRO: We are dealing with an illness that began abruptly with epileptic attacks and focal signs which suggested neoplasm so strongly that craniotomy was performed in January 1947. The illness subsided, then flared up, and nearly three years after the onset (April 1949) the patient died following a second craniotomy, this time on the opposite side. Was it a tumor after all? If so, it must have spread from one side of the brain to the other during the three-year course. This is possible with a tumor infiltrating via the corpus callosum. Yet the protocol suggests some clinical clearing rather than relentless progression during the interval between the first and second operations. Multiple tumors of metastatic origin are ruled out for the same reason, plus the long duration of the illness.

I believe we can assume that the surgeons who first explored our patient were correct in attacking the left side, for we are told that, in addition to the seizures, there was some difficulty with speech and reading and later right hemiparesis. It is true that the latter feature followed the craniotomy, raising the possibility that some of the pathology in the left cerebrum was induced surgically; but against this there is the clinical description of the course, with repetitive clearing and exacerbation of difficulties on this side of the brain.

When examined at the time of his final hospitalization (February 1949), signs of disease in the left cerebrum were noted, but there was still present a left visual field defect (homonomous in nature) and decreased sensation over the left side of the face. There can be no doubt, therefore, that we are dealing with bilaterally situated lesions, possibly multiple.

The laboratory findings on the whole are not helpful. There is no suggestion of an infectious process in the blood or spinal fluid examination. The electroencephalogram points to one side and the air studies to the opposite side.

The dilated left cerebral ventricle would indicate atrophy, probably due to infarction of the vascular system involved, and the defect on the right would indicate a swelling, prob-

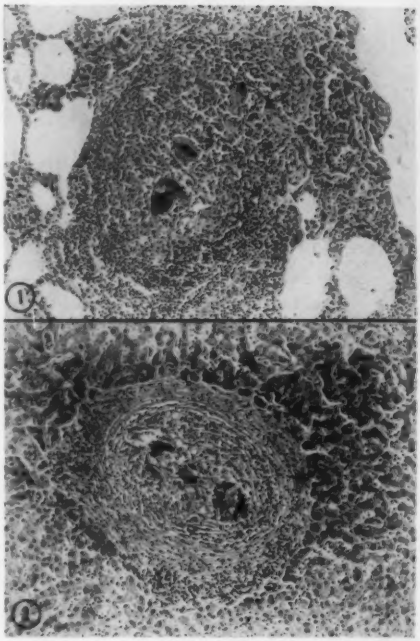

FIG. 1. Small granuloma in the lung parenchyma showing three giant cells, many epithelioid cells, with an ill-defined collar of lymphocytes. There are no ova. Hematoxylin and eosin stain.
FIG. 2. Granuloma of the liver with a central core of several giant cells and scattered epithelioid cells surrounded by a capsule of fibroblasts and lymphocytes. Hematoxylin and eosin stain.

ably a reaction to the etiologic agent. With the history of military service in the South Pacific and Philippines, one should consider the various parasites. Some of these may not cause a generalized systemic reaction, but can cause occlusion of blood vessels, granulomatous reactions, or abscess formation. A clue here is the reference to the specific therapy which was begun on the eighteenth postoperative day. In considering the various parasitic agents of this nature, the most likely would be one of the schistosomiasis variety, probably japonica, which may not give a systemic reaction and yet produces severe central nervous system pathology in the form of both infarction and abscess. In this case, with a history of service in this area of the world and with bilateral cerebral findings, I feel the most likely diagnosis is schistosomiasis, with old infarction

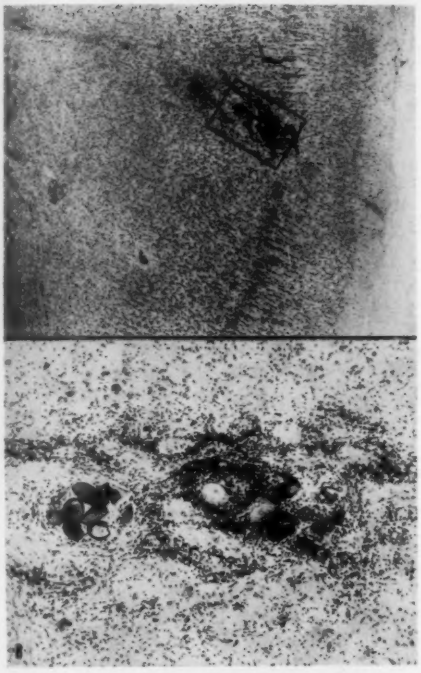

FIG. 3. A lesion involving primarily layers 4, 5, and 6 of the cerebral cortex. *A*. The neuronal architecture about the lesion has been disarranged. The deeper staining portions of the lesion are lymphocytes. The remainder of the lesion is made up primarily of young fibroblasts, often with considerable noncellular and pale staining parenchyma between them, probably due to edema. Nissl stain. *B*. Higher power view of area outlined in *A*. One group and several isolated ova are present. Nissl stain.

from occlusion of the cerebral vessels to account for the atrophy and dilatation of the left ventricle and formation more recently of an abscess in the right parietal area.

PATHOLOGIC DISCUSSION

DR. KNOX FINLEY: At autopsy both pulmonary arteries were plugged by partially organized thrombi. An organized thrombus 7 cm. in length filled the right femoral vein and extended up into the inferior vena cava. This was the apparent source of the emboli to the lung, which were the immediate cause of death. On microscopic examination, both lungs contained multiple discrete noncaseating granulomatous foci, in which were seen large mononucleated giant cells with one or two schistosoma ova within the cytoplasm (figure 1). These ova and those seen in other organs were typical of the japonicum variety. Ova were also found on microscopic examination in the periportal areas of the liver (figure 2), although this organ presented no gross abnormality other than slight congestion.

A number of fibrous adhesions and a pocket of semipurulent material lying between the dura and the calvarium were encountered under the bone flap in the left temporoparietal region. The brain weight was 1,300 gm. The vessels at the base of the brain showed no abnormality. On examination after fixation in formalin, the surface of the brain presented a diffuse but patchy granular appearance, with many areas of cortical degeneration. The cut surfaces were marked by numerous areas of degeneration and softening of both cortex and white matter. In some areas the parenchyma had a distinct granularity and a woody consistency. Throughout these areas were many black specks as though the tissue had been sprinkled lightly with pepper. Sections of the cerebellum and brainstem were grossly normal.

Histologic examination (Nissl stain) of the brain tissue showed that, for the most part, the granulomata were small, measuring 1 to 2 mm. or less in diameter. The great majority of them lay within the cerebral cortex (figures 3 and 4). Occasional granulomata were present in the white matter, usually in the subcortical white substance (figure 5). There was no predisposition for the granulomata to involve one layer of the cortex more than any other. Figure 3 illustrates lesions in the deeper layers, while figure 4 illustrates lesions located in the more superficial layers. Meningeal reaction with granulomata also occurred (figure 6). Perivascular lymphocytic cuffing was limited predominantly to the veins. This was noted particularly in veins in the deep white matter draining the adjacent cortical and subcortical sites where the primary lesions were encountered.

The granulomata varied in their appearance but often contained giant cells, with occasional ova surrounded by a zone of non-staining parenchyma with scattered fibroblast-like elements, microglia, and occasional swollen astrocytes. These granulomata were usually surrounded by an ill-defined collar of lympho-

cytes between the granuloma and the surrounding parenchyma. The parenchyma adjacent to the granuloma showed varying degrees of reaction on the part of the glial elements, particularly swelling and proliferation of microglia and astrocytes. The normal neuronal cell arrangement about the granuloma was often distorted, with varying degrees of dropping out of neurons. Other lesions presented a less granulomatous appearance, with a predominance of lymphocytes, epithelioid cells, and scattered ova, with or without giant cells.

DR. D. FRANK BENSON: There are three varieties of schistosomes or blood flukes that infect humans, *S. hæmatobium*, *S. mansoni*, and *S. japonicum*, each of which produces a distinctive disease.[1] The first usually infects the urinary bladder, while the latter two affect mainly the biliary vascular tree and the intestine. The central nervous system is not affected in the usual course of the disease. However, sporadic cases of brain involvement have been reported and a relatively large number of cases were discovered in U. S. troops serving in the Pacific in World War II. Although the majority of these cases have been caused by *S. japonicum*, it should be kept in mind that all three parasites have been known to produce central nervous system manifestations.

The organism of *S. japonicum* gains access to the human host as cercariæ which invade the skin of individuals swimming or wading in still water. The cercariæ enter the capillary bed and on reaching the liver mature and produce fertilized ova.

The first clinical symptom after invasion of the cercariæ is usually a dermatitis ("swimming itch"). This is followed by a rather insidious course of fever, malaise, cough, and abdominal complaints. The blood will show a marked eosinophilia. The second stage is often indistinguishable from the first stage. It is characterized by abdominal cramps, fever, malaise, blood and mucus in the stool, possibly diarrhea, enlargement of the liver and later the spleen, and ova in the stool. The third stage of the disease occurs years later and consists of cirrhosis, with papillomata of the intestine as a not too rare complication.

The central nervous system is not usually involved in the early stages of the clinical course of schistosomiasis. Some authors have suggested the possibility that headache seen with the fever and malaise of the early stages of the disease is due to central nervous system involvement, but this has never been proved. However, in the past 60 years a number of cases of schistosomiasis of the brain and spinal cord have been proved histologically, and there are now sufficient data to permit description of the disease process. Apparently there are two types of central nervous system involvement. The first type is that seen about five or six weeks after infection and may or may not be accompanied or preceded by the usual systemic and gastrointestinal symptomatology of this disease. The manifestations of this acute stage of central nervous system involvement commonly include headache, delirium, confusion, aphasia, amnesia, convulsions, hyperreflexia, visual disturbance, nuchal rigidity, loss of superficial reflexes, and motor weakness. These early symptoms usually subside spontaneously. The second or chronic type occurs from ten months to four years (or more?) after the original infection. The time interval is uncertain because in many cases there is no history to date the initial invasion. Again the findings are usually headache and such focal signs as mono- or hemiparesis, aphasia, or jacksonian seizures. The over-all clinical picture simulates that of a brain tumor.

The schistosome and its ova produce a marked inflammatory reaction in the central nervous system. This reaction is probably the result of a combination of infarction due to vascular obstruction, foreign protein reaction, and other noxious chemical factors.[2] This produces a granulomatous lesion which in most cases has been large and single, but in at least a few has consisted of a number of small nodules scattered through the cortical and subcortical substance. Almost all the lesions reported have been located in the parietal, occipital, or posterior temporal lobes and the majority have been subcortical. There is one report of the ova of *S. japonicum* identified in the cerebrospinal fluid taken from a lumbar tap, and one report of identification from ventricular fluid.[3] No adult worms have been reported in any of the pathologic tissues.[3]

The central nervous system is not a normal breeding ground for schistosomes. The earliest theory as to how the parasites reach the central

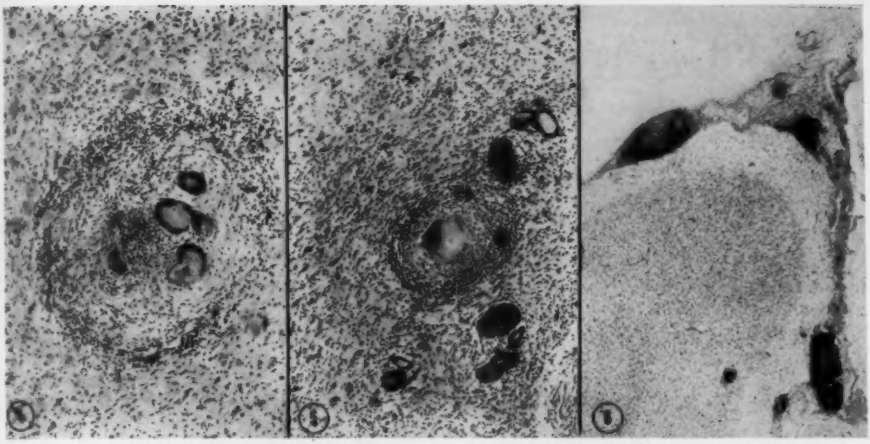

FIG. 4. A small granuloma with four giant cells in the second layer of the cerebral cortex. There are two ova, one of which appears to be partly destroyed and surrounded by one of the giant cells. There is a surrounding mesh work of fibroblasts, glial elements, and a scattering of lymphocytes. Surrounding the granuloma is an ill-defined collar of lymphocytes. Nissl stain.

FIG. 5. A lesion in the subcortical white matter with a central large multinucleated giant cell surrounded by a collar of lymphocytes and necrotic debris. Three ova lie within the collar of lymphocytes. Outside this zone are several clumps of larger ova surrounded by a loose mesh work of fibroblastic-like elements, microglia, and astrocytes. Nissl stain.

FIG. 6. Lesions of the subarachnoid space extending into the sulcus. There are two large concentrations of cellular elements, one overlying the surface of the convolutions, the other lying in the sulcus. They are made up primarily of lymphocytes, epithelioid cells, and some necrotic amorphous debris. Both contain ova, not clearly seen at this magnification. Nissl stain.

nervous system is via the blood stream as emboli. However, all the lesions appear around venules, not arterioles, and no explanation is available to pass the embolic mass through the pulmonary capillary bed. Another theory holds that the worms migrate through the venous channel against the current to reach the cerebral sinuses. But, as noted above, no worms have been noted in any of the pathologic studies and it has been proved that the parasites will not develop outside the hepatic system.[4]

Diagnosis in the early stage of the disease should be suspected if the patient has recently been in an endemic area, if the blood count shows an eosinophilia, and if ova can be found in the stool. During the late stage these are of little help. Although the patient may give the history of having been in an endemic area, he frequently will have no history of an acute infection, there will be no eosinophilia in the late stage, and ova will probably not be found in the stool. During this late stage the picture will resemble a space-occupying lesion, and there is probably no way to differentiate this condition from a neoplasm or granuloma other than surgical exploration with pathologic proof of the organism.

When the diagnosis is made, specific chemotherapy is available. Antimony products have been the drugs of choice and in military experience, antimony potassium tartrate (tartar emetic) is the most effective. If this cannot be tolerated, stibophen (Fuadin) should be used. The treatment should be carried to tolerance and repeated if there is any recurrence of ova in the stools. In treatment of the late stage, craniotomy with biopsy and decompression, followed by specific chemotherapy, is the treatment of choice. Results of treatment have generally been good, with complete or nearly complete recovery the general rule.

REFERENCES

1. MACKIE, T. T., HUNTER, G. W., and WORTH, C. B.: A Manual of Tropical Medicine, ed. 1. W. B. Saunders Co., Philadelphia, 1945, pp. 372-391.
2. KANE, C. A., and MOST, H.: Schistosomiasis of the central nervous system. Experiences in World War II and a review of the literature. Arch. Neurol. & Psychiat. 59:141, 1948.
3. Carmichael, F. A., JR., and COWLEY, H. S.: Schistosomiasis of the brain. J. Neurosurg. 9:620, 1952.
4. FAUST, E. C., and MELENY, H. E.: Studies on Schistosomiasis japonica. Am. J. Hyg. 1924, Monograph series No. 3, xii, 339 pp.

CASE REPORT

Silent Hydrocephalus

Edwin Clarke, M.D., M.R.C.P. and
John Laidlaw, M.B., M.R.C.P.E.

FOR MANY YEARS the function of the cerebral hemispheres has proved to be a fascinating problem which is as yet unsolved. Authorities differ as to fundamental mechanisms, but few would question the importance of this part of the brain in man. It would be surprising if an apparently normal individual could be shown to have a grossly reduced amount of cerebral substance. The subject of this report is such a case.

CASE REPORT

A French-polisher aged 36 was seen on September 27, 1955 in the outpatient department. He had suffered mild and occasional headaches for about two years but recently they had become more severe. The pain was throbbing, vertical, and at times associated with nausea. It was influenced by his emotions, but it did not interfere with his work or with his domestic and social activities. He had suffered no severe illnesses, but he had been deaf since exposure to gunfire during the war.

On examination he was anxious but of apparently normal intellect. Apart from some pallor of the optic disks (visual acuity and fields normal) and bilateral high tone deafness, the nervous system was normal. Other systems were likewise intact. Although it was thought that he was suffering from an anxiety state for which there was adequate cause, a roentgenogram of the skull was carried out. This showed normal shape and size, but the convolutional markings of the cranial vault were increased. There was enlargement of the pituitary fossa and erosion of the posterior clinoid processes, suggesting destruction from without. As a result, admission was advised and the following investigations performed.

Cerebrospinal fluid. The pressure and contents were normal.

Electroencephalogram. There were no localized or paroxysmal abnormalities. The alpha rhythm was well developed, with regular wave form and many well-marked spindles. There was little polyrhythmia and the dominant frequency was 9 cycles per second. Waves of alpha frequency and form synchronous with the alpha rhythms were prominent precentrally. Although the alpha rhythm was reduced on opening the eyes and increased by closing them, it tended to reappear and to become quite prominent four to five seconds after eye opening (figure 1).

When the patient was receiving a small sedative dose of barbiturate, low to moderate amplitude fast activity was clearly seen anteriorly (figure 1), and during the induction of sleep by intravenous thiopentone this fast activity dominated the record (figure 2).

Over-breathing evoked moderate to high and high amplitude generalized delta waves, which showed approximate bilateral synchrony and symmetry (figure 3). At first these waves occurred singly, but during the course of over-breathing they became organized into short runs.

Air encephalography. When 60 ml. of air were fractionally introduced into the lumbar subarachnoid space, gross symmetric dilatation of the whole ventricular system was demonstrated (figures 4, 5, and 6). Enlargement of the lateral ventricles seemed to be greatest posteriorly (figure 6) and there was severe thinning of the whole cerebral mantle.

Psychometric examination. After detailed testing it was assumed that he had always had an inferior memory, as evidenced by his poor scholastic attainment. His general intellectual function and in particular his reasoning powers were within normal limits. The intelligence quotient on both verbal scale and vocabulary test was 94.

Neuro-otologic examination. Severe bilateral high tone deafness characteristic of acoustic trauma was found, but the vestibular functions were normal.

Progress. He has now been observed for over two and a half years and his condition has remained much the same. He still has occasional bouts of headache but they are not severe. There has been no change in his nervous system. A total of five routine electroencephalograms made between October 1955 and July 1957 have shown no significant variation.

Comment. It is clear that, despite a remarkable degree of hydrocephalus, this man appeared normal on routine clinical examination, and it was only the radiologic investigations which revealed the true state of affairs. He is a skilled craftsman and any difficulties that he may experience in living a normal

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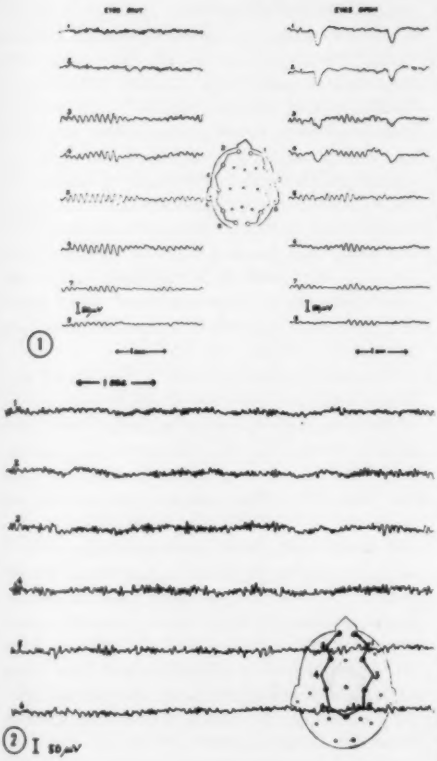
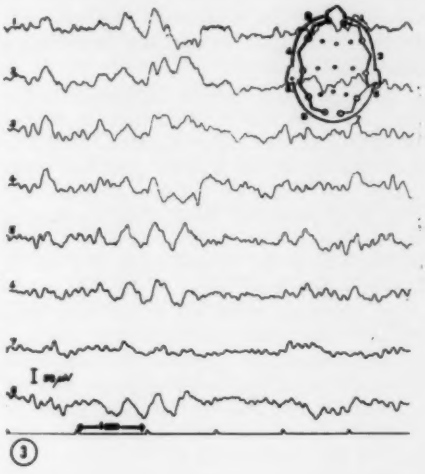


FIG. 1. Routine electroencephalogram, resting record with eyes shut and open. Patient was receiving a small dose of barbiturate at the time.

FIG. 2. Electroencephalogram after intravenous thiopentone.

FIG. 3. Electroencephalogram within a few seconds of stopping three minutes of overbreathing.



life are due either to his wife's irascibility or to his deafness. Even a more detailed study of his mental and physical functions did not reveal the defects which might have been expected in the presence of massive hydrocephalus. His intellect, although limited, cannot be considered to be much below the average for the position in society to which he belongs. His literary tastes suggest that he may even be in advance of his colleagues; his favorite book is an early edition of "Aids to Physiology."

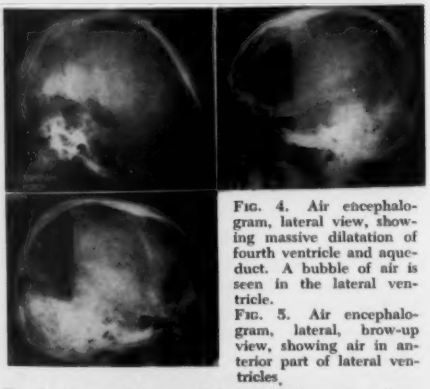


FIG. 4. Air encephalogram, lateral view, showing massive dilatation of fourth ventricle and aqueduct. A bubble of air is seen in the lateral ventricle.

FIG. 5. Air encephalogram, lateral, brow-up view, showing air in anterior part of lateral ventricles.

FIG. 6. Air encephalogram, lateral, brow-down view, showing air in posterior part of lateral ventricles.

DISCUSSION

The lesion responsible for the hydrocephalus could not be demonstrated with certainty in this case. Since the symptoms were mild and the likelihood of finding a remediable lesion slight, it was felt that further investigations were not justified. In view of the greatly dilated fourth ventricle (figure 4), however, it seems likely that there is an obstruction to the flow of cerebrospinal fluid from the ventricular system by way of the foramina of Luschka and of Magendie. A congenital atresia of these exits has been described by Taggart and

Walker[1] and by others on many occasions since. A similar condition may result from postmeningitic arachnoidal adhesions in the same region, but a clear history of meningitis is not necessarily obtained in these patients.[2] The blockage in our patient is presumably incomplete, and his intermittent headache may be due to episodes of increased intraventricular pressure.

In infants with chronic obstructive hydrocephalus it has been found possible to employ the degree of ventricular dilatation – and thus the thickness of the cerebral grey and white matter – to estimate intellectual potential.[3] This is of particular value when considering surgical procedures to relieve the hydrocephalus, for only if the cerebral tissue is 2 cm. or thicker is the child likely to develop an average intellect. However, it has long been known[4] that when hydrocephalus develops slowly a correlation between the degree of ventricular expansion and intelligence does not necessarily exist. Several authors have remarked that persons with considerable thinning of the cerebral mantle may appear superficially to be physically and psychologically normal.[5,6] Dandy[7] mentioned advanced hydrocephalus in children who were "seemingly mentally almost normal – at times even precocious in some respects at the age of three, four, and five years." It is interesting here to note that Ford[5] has found abnormally acute auditory memories in blind hydrocephalics. Another child with hydrocephalus and minimal mental changes had an intelligence quotient of 94 when two and a half years old and at age eight was "vivacious, alert, and polite." Some of the children with gross ventricular expansion and normal mentality may survive, and there are several reports in the literature of patients similar to ours. Scarff[8] described two cases where severe hydrocephalus was found in persons who had been considered normal previously. One was a woman of 40 who had been a school teacher for 20 years, yet the tissue of her cerebral hemispheres had an average thickness of only 2.5 cm. The other at the age of 26 "appeared normal in every respect." Again, a man of 39 who had always been accepted as normal intellectually died of an acute infection and was at autopsy found to have "a considerable degree of hydrocephalus."[2]

As well as being surprisingly intact intellectually, these patients usually have few physical defects and it is a common experience to find a normal nervous system.[5,7] In addition, the head may be of normal size, as in our patient, presumably because of the very slow development of the ventricular dilatation. It was possible to demonstrate that the opticokinetic and caloric responses were normal in our case, thus proving that the complex pathways in the cerebral hemispheres and brainstem subserving these functions[8] were intact. Furthermore, the electroencephalogram was remarkably normal.

Neurophysiologists, working with data from animals under experimental conditions and occasional human operation material, have been unable to agree on the source of the spontaneous rhythmic electrical activity recorded from the brain.[9–11] That certain rhythms may be recorded from artificially isolated areas does not prove that these areas are the source of such or similar rhythms in the intact human brain.[12,13] It seems probable that the spontaneous rhythms recorded from scalp electrodes represent the synchronized activity of large cortical neuronal populations and that these rhythms are influenced both by cortical activity and by specific and nonspecific projections from the diencephalon.[14] It is not to be expected that the findings in a single case would contribute much to this complex problem, but it is of interest to record prominent alpha (figure 1) and fast activity (figure 2) similar to that found in normal people from a patient with very greatly reduced cerebral substance. It might be speculated whether the regularity of the alpha rhythm, its extent precentrally, and its reappearance with the eyes open (figure 1) represent a failure of desynchronization due to reduced cortical activity, and whether the over-breathing response (figure 3), which would be considered normal in a younger person, might be due to a failure of maturation.

The finding of an essentially normal electroencephalogram in the presence of gross cerebral pathology serves to emphasize the significance of "a normal electroencephalogram." Most electroencephalographic abnormalities are not a function of structural changes in the brain but of the disordered metabolism of

living nerve cells. Abnormalities may be produced by generalized biochemical factors which affect the whole or a part of the brain or by local lesions such as tumors or cicatrices, if they interfere with the metabolism of a sufficient number of contiguous neurons. A small actively growing and infiltrating tumor can produce a gross localized abnormality, whereas a comparatively large area of old infarction may produce none. It follows, therefore, that a normal electroencephalogram provides evidence, not that the brain is normal, but that there is no considerable group of viable nerve cells whose function is being impaired by any localized or generalized pathologic process. In our case the normal electroencephalogram, which was paralleled by normal physical and psychologic findings, demonstrates the success with which the relatively small amount of residual nervous tissue has adapted to the gross changes in cerebral structure consequent on a chronic lesion.

This adaptation may be due in part to the deeper structures such as the basal ganglia, the brainstem, and the parts between, taking a more active role in brain functioning. Thus, it is possible that they can carry out motor tasks which are usually considered the prerogative of the cerebral cortex. It is common knowledge that an anencephalic monster can move its limbs, and a remarkable case reported by Puech and associates[15] indicates what can be expected if a child almost completely lacking in cerebral cortex survives infancy. Their patient was considered normal at birth, but the head became moderately enlarged and, despite the fact that there were no cerebral hemispheres, she had a normal physical development and some emotional reaction. Limb functions, special senses, and general sensation, although probably abnormal, were at least present, and the electroencephalogram was considered normal for her age. Similar cases have also been described.[16–19] In addition to the motor functions carried out by diencephalic structures, McFie and Piercy[20] have recently pointed out that the thalamus may play a role equal to, or even greater than, that of the cerebral cortex in mental performance.

In our patient there is no doubt also that some functioning of the cerebral cortex remains, as well as brainstem activity. If the cerebral hemispheres are normal at birth and if the cortical thinning is slow enough in its development, presumably considerable function as detected by psychologic, physical, and electrical methods will remain. The critical level of neuron population is unknown and so far it has not been reached in our patient, if the condition is progressive.

Recent work on hemispherectomy has proved that cerebral function can be crowded into one hemisphere, and the present case, together with others like it, shows that the brain can still function in a manner which is remarkably normal even when gross deformities exist. It further indicates that the brain is an adaptable organ and, as Sherrington pointed out long ago, it behaves in a highly integrated fashion. Furthermore, as Goody and Reinhold[21] maintain, intellectual capacity is more likely to be a function of the activity rather than the size of the brain.

SUMMARY

A case of chronic hydrocephalus with enormous ventricular dilatation is reported. Despite the severe brain deformities, very few mental, physical, or electroencephalographic abnormalities were detected. The possible explanations for this are discussed. It is emphasized that a chronically distorted brain may still function as an integrated whole.

REFERENCES

1. Taggart, J. K., and Walker, A. E.: Congenital atresia of the foramens of Luschka and Magendie. Arch. Neurol. & Psychiat. 48:583, 1942.
2. Russell, D. S.: Observations on the Pathology of Hydrocephalus. H. M. Stationery Office, 1949, case 1, p. 13.
3. Scarff, J. E.: Nonobstructive hydrocephalus. Treatment by endoscopic cauterization of the choroid plexus. Long term results. J. Neurosurg. 9:164, 1952.
4. Gintrac, E.: Mémoires et Observations de Médecine Clinique et d'Anatomie Pathologique. C. L. Neveu, Bordeaux, 1830, p. 220.
5. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence. Springfield, Illinois, Charles C Thomas. 2nd ed., 1944, p. 236.
6. Pennybacker, J.: Obstructive hydrocephalus. Ann. Roy. Coll. Surgeons England 12:51, 1953.
7. Dandy, W.: Hydrocephalus. In Lewis: Practice of Surgery, Hagerstown, Maryland. Vol. 2, 1947, p. 202.
8. Carmichael, E. A., Dix, M. R., and Hallpike, C. S.: Lesions of the cerebral hemispheres and their effects upon optokinetic and caloric nystagmus. Brain 77:345, 1954.
9. Müller-Limmroth, W., and Caspers, H.: Theorien

über den Entstehungsmechanismus der Spontanrhythmen im normalen Elektrencephalogramm. Klin. Wchnschr. 34:337, 1956.
10. Bremer, F.: Considerations sur l'origine et la nature des "ondes" cérébrales. EEG & Clin. Neurophysiol. 1:177, 1949.
11. Brazier, M. A. B.: Physiological mechanisms underlying the electrical activity of the brain. J. Neurol., Neurosurg. & Psychiat. 11:118, 1948.
12. Morison, R. S., and Bassett, D. L.: Electrical activity of the thalamus and basal ganglia in decorticate cats. J. Neurophysiol. 8:309, 1945.
13. Chatfield, P. O., and Dempsey, E. W.: Some effects of prostigmine and acetylcholine on cortical potentials. Am. J. Physiol. 135:633, 1942.
14. Bishop, G. H.: Potential phenomena in thalamus and cortex. EEG & Clin. Neurophysiol. 1:421, 1949.
15. Puech, P., Guilly, P., Fischgold, H., and Bounes, G.: Un cas d'anencéphalique hydrocéphalique. Etude électro-encéphalographique. Rev. neurol. 79:117, 1947.
16. Edinger, L., and Fischer, B.: Ein Mensch ohne Grosshirn. Arch. ges. Physiol. 152:535, 1913.
17. Casamajor, L.: A child without a forebrrain. Tr. Am. Neurol. A. 63:64, 1937.
18. Johnson, E. E., Warner, M., and Simonds, J. P.: Total absence of the cerebral hemispheres. Report of two cases. J. Pediat. 38:69, 1951.
19. Kuhlenbeck, H., Maher, I., Ross, M., and Eastwood, R.: Hydranencephaly with univentricular telencephalic malformation (General comments, with anatomical and clinical observations on three cases). Confinia neurol. 17:100, 1957.
20. McFie, J., and Piercy, M. F.: Intellectual impairment with localized cerebral lesions. Brain 75:292, 1952.
21. Goodby, W., and Reinhold, M.: The functions of the cerebral cortex. Brain 77:416, 1954.

■ The doctrines of Gall and Spurzheim have been very differently estimated by different physiologists; some speaking of them in terms of high commendation, others treating them with great contempt. Their mode of dissecting the brain, however, seems to have been pretty generally approved. Dr. Leach, in a letter to Mr. Forster, says, "What Dr. Spurzheim has asserted respecting the structure of the brain, is perfectly correct, and this structure may be seen by any anatomist who may be disposed patiently to examine that organ after the mode directed by Dr. Spurzheim." The commissioners of the French Institute, appointed to examine the memoir of Dr. Gall on this subject, allow that these anatomists have pointed out new methods of dissecting the brain, new connections and directions perceived between the different masses, and the organic elements which compose them, and new peculiarities in some of their parts.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

CASE REPORT

Abnormalities in offspring related to maternal rubella during pregnancy

Anatole Dekaban, M.D., James O'Rourke, M.D. and Tillye Cornman, M.D.

In 1941 Gregg[1] made the original observation that rubella during the early stages of pregnancy can cause damage to the fetus. Subsequently, a number of other authors[4–6] reported similar cases. The chief abnormality encountered in the newborn infant consists of congenital lesions involving various body organs. It has been suggested that the type of anomaly may depend on the stage of gestation when the rubella infection took place.

We are reporting a patient who showed almost all abnormalities ever described in association with maternal rubella. The eye findings, results of surgical excisions of cataracts at a widely separated interval, and his general state warrant more detailed consideration. In addition, on the basis of 108 cases selected from the literature, an attempt is made to correlate and analyze more closely the occurrence of various lesions in different organs with the stage of gestation when rubella complicated the pregnancy.

CASE REPORT

An eight year old boy was a first child born to young parents. His mother developed severe rubella at the end of the fourth week of gestation and had to be confined to bed for one week. She suffered from sore throat, general malaise, enlargement of the glands in the back of her neck and in the axillae, and also a reddish rash involving her face and trunk. Several cases of rubella occurred about the same time in the immediate neighborhood. The family physician who diagnosed the disease was not aware that she was pregnant. A few weeks later this became obvious and the age of gestation was estimated. Apparently, the risk of possible damage to the fetus was realized. She had routine prenatal care and the course of her pregnancy was uneventful. Delivery took place at term under general anesthesia. No difficulty was encountered with the infant's breathing, but his head was noted to be small, he had bilateral cataracts, and there was a blowing systolic murmur in the pulmonic area. At the age of five months extraction of the cataract from the right eye was performed. The final result of this operation was not satisfactory, however.

The development of the patient was retarded from his first months of life. He was not able to lift his head up in prone position until several months old. He began to roll over at the age of about 15 months. With marked sagging of his back and dropping down of his head, he first sat up when three years of age. At the age of seven years he began to pull himself up to a standing position on his toes. He never showed an appropriate response to auditory or visual stimuli. Psychologic examination at the age of one year and three months gave him the mental age of about three months. In his second year of life he was confined to the District Training School in Laurel, Maryland.

The authors examined him at the age of seven and a half years. His height and state of nourishment were normal. He spent most of his time lying down, although he could sit without support with sagging of his back for about half an hour. No abnormality was detected in the lungs and abdomen. The heart was slightly enlarged in the transverse diameter. The pulse was regular, 86 per minute. There was a grade III, harsh systolic murmur best heard left of the sternum. The head was small and rounded, its circumference being 48.5 cm. (normal for his age is 53 cm.). Both external ears were formed defectively. Generally he was quiet and cheerful and appreciated any attention given to him by means of tactile stimulation. He laughed aloud to himself or when handled; otherwise, apart from an occasional shrill noise, he had no vocalizations. When supported he would stand briefly on his tiptoes and attempt a few steps (figure 1). He manipulated toys and showed some persistence in tactile exploration of his surroundings. Clean habits were not acquired and he had to be fed. Because of auditory and

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visual deprivation, it was felt useless to apply any formal psychologic testing. However, it was obvious that he functioned below the level of a 12 month old infant.

Special senses. Vision. The right eye showed buphthalmos associated with secondary glaucoma, the cornea being grossly enlarged and opaque. The left eye showed a slight reduction in the diameter of the cornea (9 mm.), but a normal anterior chamber, clarity, and depth. Generally it was a microphthalmic eye. On ophthalmoscopic examination the cornea appeared clear and showed free margins, but the lens was completely occluded by a white opaque cataract of undetermined thickness which prevented funduscopic examination. There seemed to be just a trace of visual perception in this eye, for he lifted the left upper lid maximally and turned his head upward and to the left when a strong source of light was presented. However, there was no indication that he could see any objects.

Hearing. Drums were intact. Hearing was grossly defective in both ears. No response was obtained to loud ringing of a bell from a distance of one meter. Ringing close to either ear would make him cease his activity momentarily.

Caloric test. The response to irrigation with cold and hot water was delayed and the duration of nystagmus shortened; it lasted one minute and ten seconds in the right ear and one minute and five seconds in the left ear, as estimated from the onset of stimulation.

Taste. He differentiated well between salt and sugar and between pleasant and disagreeable substances.

Smell. He accepted coffee and clover but inconstantly rejected asafoetida.

Cranial nerves. Eyeballs could be moved in all directions. Their relative position was as symmetric as might be expected in a blind person. Remainder of the cranial nerves were normal.

Motor system. He had contractures of Achilles tendons and his feet were in an equinovarus position. Active movements in all joints could be performed, but the muscle power was generally decreased. When supported, he could stand for several minutes in an awkward position; then the hip and knee joints buckled and he slipped to the ground. He rolled and crept actively.

Coordination. No routine tests could be applied because of the lack of cooperation. During spontaneous and induced movements there was no tremor or decomposition of movements.

Sensation. He readily responded to the stimuli of light touch, pain, and temperature throughout his body; other modalities could not be tested.

Reflexes. All tendon reflexes were brisk and equal, except for ankle jerks which were hypoactive because of tendon contractures. Plantar response was flexor on both sides.

Laboratory tests. Urinalysis, Kahn test, cerebrospinal fluid, and blood studies were all within normal limits. Tests for toxoplasmosis and phenylpyruvic acid were negative. Radiologic examination of the skull revealed its smallness in all dimensions (figure 2) but no other pathology. Maturation of bones was normal for his age. Electroencephalogram showed fairly well developed alpha activity in the range of 7 to 9 cycles per second. In addition, there were infrequent slower rhythms recorded diffusely. The tracing was interpreted as borderline normal. Pneumoencephalogram disclosed a symmetric and normal size ventricular system and symmetric distribution of air in the subarachnoid space (figure 2). The electrocardiogram was consistent with left axis deviation and sinus arrhythmia.

Clinical diagnosis. Microcephaly, deafness, congenital cataracts, secondary glaucoma with buphthalmus of the right eye, congenital heart disease (probably interventricular defect), and marked mental retardation, all related to maternal rubella during the early stage of gestation. The severe degree of mental deficiency was probably due to combined causes: effects of rubella, together with deprivation of eyesight and hearing. It was felt that removal of the cataract in the left eye could benefit the patient's vision.

A linear extraction of the cataract in the left eye was attempted under general anesthesia. With keratome section of the superior limbus, the point of the blade was allowed to penetrate the cataract surface. At this stage it was discovered that the opacity consisted of a tense, white membrane without cortical content. As the membrane edges retracted, an opening was established which was equal to two-thirds of the total pupillary area. Particles of lens debris were removed by irrigation and the wound was closed.

A fundus examination made through the new opening revealed the following findings: the vitreous was clear and the nerve head was definitely pale, particularly at its temporal margin; in addition, there was peripheral narrowing of the arterioles and a granular pigmentation scattered throughout the posterior fundus, mainly in the paramacular area (figure 4). The pigment was of granular type and did not appear to have any configuration similar to that of an established retinitis pigmentosa. The macular reflex was diminished and the foveal reflex abolished.

The patient was rechecked eight months later at the age of eight years. In general, his motor ability progressed very little. However, he was able to walk for a longer distance when led, perhaps up to 20 feet, and would pull himself up to the standing position on the radiator in order to get stronger visual stimulus from the light coming through the window. Ophthalmologic examination gave findings essentially similar to those seen immediately following the operation (figure 3). Electroretinogram at this time was normal.

DISCUSSION

The most common abnormalities encountered in the offspring of mothers who had ru-

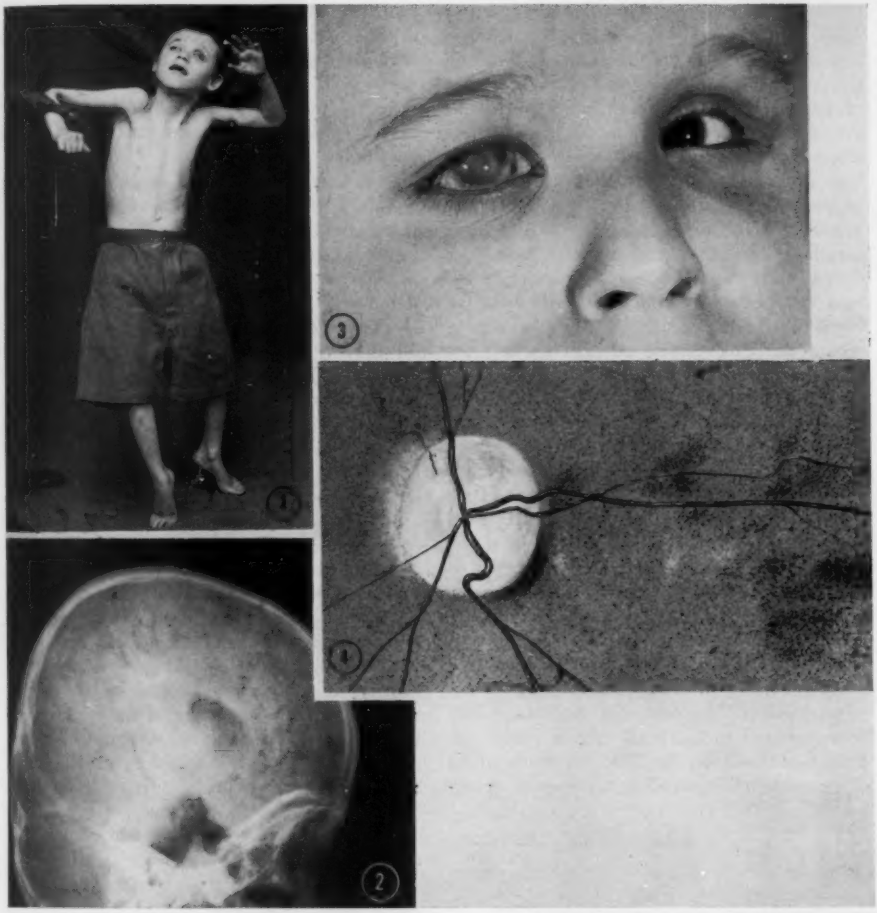

FIG. 1. At the age of eight years the patient was able to stand and walk for a short distance on his tiptoes when supported.
FIG. 2. Pneumoencephalogram, brow-up lateral projection. Smallness of skull in the anteroposterior dimension is apparent. The ventricular system and subarachnoid space are within normal limits.
FIG. 3. The right eye shows buphthalmos and corneal opacity. The left eye after excision of the cataract at eight years of age.
FIG. 4. Left optic fundus. The optic nerve is pale. The retina is thin and contains fine granular pigment, predominantly in the paramacular area.

bella during early gestation include congenital cataracts, congenital heart disease, perception deafness, microcephaly, and coexistent mental deficiency. Less frequently seen are other conditions such as microphthalmos, buphthalmos, retinal lesions, talipes equinovarus, syndactyly, hypospadiasis, generalized muscular weakness, cerebral diplegia, and cleft palate. Dental abnormalities are probably quite common, although they are seldom looked for. The affected infants generally show various combinations of several of these conditions and it is uncommon to find only one single lesion.

In the patient reported here the association of two particular features is of interest. The first is the very profound disturbance of em-

bryonic development which resulted in as many as 11 out of the total of 15 pathologic lesions recorded in the literature. The second feature relates to the unusually severe course of the rubella which complicated pregnancy very early, that is before the end of the fourth week of gestation. The occurrence of more severe abnormalities during the earliest stages of pregnancy and the substantial decline of incidence of malformations after two to three months of gestation were stressed by Swan,[2] Gregg and co-workers,[3] and others. It appeared important to us to analyze the frequency with which the abnormalities in various organs are encountered relevant to different stages of gestation. For this purpose the available literature was surveyed, but only those cases were accepted in which there were adequate data regarding the medical condition of the patient and the stage of pregnancy when rubella occurred. These criteria were met by 108 cases selected from reported series.[2,3,5–14] To make the analysis easier the data obtained from this material were plotted in a form of a graph (figure 5). It is apparent that the highest incidence of three major abnormalities in offspring, namely cataracts, congenital heart disease, and deafness, occurred when rubella complicated the first four weeks of pregnancy. However, the embryos which were exposed to maternal infection with rubella virus between the fifth and tenth weeks of gestation still showed quite frequent occurrence of these malformations. There was a rapid decline of fetal susceptibility to the effects of maternal rubella from the tenth week of gestation and it came to a very low figure at 14 weeks of pregnancy; no instances of fetal abnormality were encountered past 20 weeks of gestation.

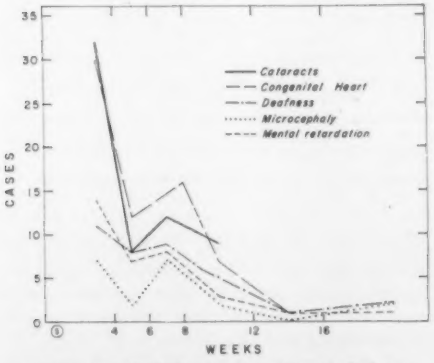

FIG. 5. One hundred and eight patients who had various congenital abnormalities associated with maternal rubella during pregnancy are plotted in relation to the stage of gestation when damage occurred.

It is known from experimental studies that the most easily damaged are those regions of the embryo in which cell proliferation is particularly active at the time of exposure to a noxious factor. By the end of the fifth gestation week differentiation of the three primary layers into organs is completed and from then on the organs undergo independent growth and organization. The highest incidence of malformations coincides with this earliest stage of primary formation of organs. It is likely that a greater intensity of teratogenic agents is necessary to induce similar malformations in later stages of gestation. This would explain the reduced occurrence of abnormalities in infants whose mothers had rubella between six and 12 weeks of pregnancy. Another interesting question relates to the fact that more profound damage probably results from exposure to a greater severity of the rubella infection, even during the earliest stages of gestation. This conceivably may account for the variability in the clinical picture of the affected infants, as well as for the fact that not all products of pregnancy complicated by rubella, even during the earliest stage, develop congenital lesions. However, the incidence of non-affected infants could not be estimated from this material.

In general, the frequency with which cataracts, congenital heart disease, and deafness occurred during the first ten weeks of gestation was quite congruous. However, no instance of cataract was encountered in association with maternal rubella past ten weeks of gestation. Also, the numerical incidence of deafness during the first four weeks of pregnancy was less than that of cataracts and congenital heart disease. This may be related to the fact that milder forms of deafness are more difficult to detect on routine clinical examination than, for example, cataract or heart murmur. The most frequent type of congenital heart disease was patent ductus arteriosus and persisting foramen ovale. Microcephaly and mental de-

ficiency showed considerably lower incidence than cataracts and congential heart disease. In our opinion this is unlikely to be a true state. A proportion of patients included in this analysis were very young infants in whom the examining physician would not be confronted with evidence of milder forms of mental retardation. Similarly, unless of a severe degree, smallness of the head would be easily missed on routine examination.

The mechanism and detailed pathology of the described lesions are poorly understood. No comprehensive postmortem examinations of the central nervous system are available to allow the formation of reasonably objective concepts. Experimental evidence from another type of diffuse damage to the fetus[13] suggests the possibility of selective damage to proliferating cells of the particularly sensitive structures during early embryonal life. Simple arrest or delay of development during a particular phase in organ differentiation is less likely.

Considered in terms of vision restored, the results of congenital cataract surgery are less pleasing than those which follow removal of the senile lens. There appear to be two main reasons for this state: 1) a not uncommon association with other congenital abnormalities involving the retinae, optic nerves, or eyeball, and 2) a relatively frequent postoperative complication, such as secondary glaucoma, pupillary occlusion, and retinal detachment.[16] Falls[17] and Costenbader and associates[18] are of the opinion that linear extraction technic with removal of the contents of the lens in toto lessens the danger of complications.

The membranous cataract encountered in the present case is uncommon and represents complete intrauterine absorption of intracapsular lens parenchyma so that the remaining capsule forms a thin, dense, white sheet. More typical of the postrubellar lens is a cataract of the zonular variety whose dense, central opacity completely fills the pupillary opening; when examined with the pupils dilated, the central whiteness is seen enclosed by a thin zone of gray opacified cortex, peripheral to which the cortex is clear. When macular changes are not severe, an early operation will permit normal development of fixation reflexes, thus offsetting the occurrence of ocular nystagmus. The type and size of the opacity in postrubellar cataract depend largely on the state of lens development at the time of damage.[19] Surgery is not indicated in all cases of congenital cataracts, the decision depending mainly on the degree of vision permitted by the opacity. When mydriasis materially improves visual acuity, an optical iridectomy will often suffice and cause fewer complications.[18]

Following surgery on the left eye, the ophthalmoscopic examination revealed pallor of the optic disk and a dispersion of fine, pigmented spots in the retina, with predominant involvement of the macular region. Dispersion of pigment of this type on the postrubellar fundus has been named pseudoretinitis pigmentosa.[20] The distinguishing feature of the true retinitis pigmentosa is the presence of arteriolar narrowing and perivascular collection of pigment.

From the practical viewpoint, early management of the affected infants is important. A considerable proportion of these patients are born with lowered intellectual capacity (usually of mild degree) which can conceivably be related to primary dysfunction of the brain. Gross impairment of vision and hearing, if present, will further handicap development and may lead to a very severe degree of mental deficiency amounting to idiocy. Comprehensive and timely medical assessment during infancy, removal of cataracts, provision of a hearing aid whenever indicated, and institution of appropriate devices will increase the patient's chance to remain in the family and even may allow him to attend a regular school.

SUMMARY

A patient is described who suffered multiple congenital abnormalities as a result of maternal rubella during the fourth week of gestation. The results of various laboratory tests are outlined. Operation on the right congenital cataract at the age of five months was unsuccessful. The left cataract was removed at eight years of age and clear eye media were obtained; this, however, did not result in a significant increase of the functional vision. The need for early treatment of children suffering from a similar condition is stressed.

One hundred and eight patients with evidence of damage from maternal rubella were selected from the literature and their condi-

tion analyzed in respect to the stage of gestation when rubella infection took place. It was found that the highest incidence of the three most important congenital anomalies (cataracts, deafness, and congenital heart disease) occurred when rubella complicated pregnancy during the first five weeks of gestation. The occurrence of malformations in later stages of pregnancy was analyzed. The most common types of cataracts encountered in this condition, as well as general management of the affected infants, were discussed.

REFERENCES

1. Gregg, N. M.: Congenital cataract following german measles in the mother. Tr. Ophth. Soc. Australia 3:35, 1941.
2. Swan, C.: Study of three infants dying from congenital defects following maternal rubella in early stages of pregnancy. J. Path. & Bact. 56:289, 1944.
3. Gregg, N. M., Beavis, W. R., Heseltine, M., Machin, A. E., Vickery, D., and Meyers, E.: The occurrence of congenital defects in children following maternal rubella during pregnancy. M. J. Australia 2:122, 1945.
4. Caruthers, D. G.: Congenital deaf-mutism as sequela of a rubella-like maternal infection during pregnancy. M. J. Australia 1:315, 1945.
5. Beswick, R. C., Warner, R., and Warkany, J.: Congenital anomalies following maternal rubella. Am. J. Dis. Child. 78:334, 1949.
6. Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B.: Congenital defects in infants following infectious diseases during pregnancy, with special reference to relationship between German measles and cataract, deaf-mutism, heart disease and microcephaly, and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities. M. J. Australia 2:201, 1943.
7. Gregg, N. M.: (Further observations) congenital defects in infants following maternal rubella. Tr. Ophth. Soc. Australia 4:119, (1944) '46.
8. Evans, M. W.: Congenital dental defects in infants subsequent to maternal rubella during pregnancy. M. J. Australia 2:225, 1944.
9. Erickson, C. A.: Rubella early in pregnancy causing congenital malformations of eyes and heart. J. Pediat. 25:281, 1944.
10. Reese, A. B.: Congenital cataract and other anomalies following German measles in mother. Am. J. Ophth. 27:483, 1944.
11. Albaugh, C. H.: Congenital anomalies following maternal rubella in early weeks of pregnancy, with special emphasis on congenital cataracts. J.A.M.A. 129: 719, 1945.
12. Watson, J. R. H.: Hepatosplenomegaly as a complication of maternal rubella: A Report of 2 cases. M. J. Australia 1:516, 1952.
13. Lindsay, J. R., Caruthers, D. G., Hemenway, W. G., and Harrison, M. S.: Inner ear pathology following maternal rubella. Ann. Otol. Rhin. & Laryng. 62:1201, 1953.
14. Kirman, B. H.: Rubella as a cause of mental deficiency. Lancet 269:1113, 1955.
15. Hicks, S. P.: Developmental brain metabolism; effects of cortisone, anoxia, fluoroacetate, radiation, insulin and other inhibitors on embryo, newborn and adult. Arch. Path. 55:302, 1953.
16. Cordes, F. C.: Failure in congenital cataract surgery. Am. J. Ophth. 43:1, 1957.
17. Falls, H. F.: Developmental cataracts; results of surgical treatment of 131 cases. Arch. Ophth. 29:210, 1943.
18. Costenbader, F. D., and Albert, D. G.: Conservatism in the management of congenital cataract. Arch. Ophth. 48:426, 1957.
19. Swan, C.: Section II in A. Sorsby: Systemic Ophthalmology. Mosby, St. Louis, 1951, p. 34-44.
20. Franceschetti, A., and Bourquin, J. B.: Rubéole pendant la grossesse et malformations congénitales de l'enfant. Ann. d'ocul. 179:623, 1946.

■ Under the head of diseases of the spinal cord there is no lack of subjects. As of primary importance may be mentioned spinal meningitis, myelitis, spinal congestion, tetanus, and spinal irritation; as of secondary importance, locomotor ataxy, reflex paraplegia, infantile paralysis, hysterical paralysis, hemorrhage, white softening, induration, atrophy, hypertrophy, tumour, concussion, compression, vertebral caries, spina bifida, &c.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Neurology

BOOK REVIEWS

A Frontal Section Anatomy of the Head and Neck

O. F. Kampmeier, A. R. Cooper, T. S. Jones. 1957. Urbana, Illinois: University of Illinois Press. 68 pages. $15.00.

THIS is a superb work. The authors present, by photographic portrayal, 20 frontal frozen sections of a human head and neck in full scale. Employing BNA nomenclature, the labels are printed out in full, making reference quick and sure. An excellent choice of structures is made so that the illustrations are uncluttered by excessive lines and type. Use of the natural scale in reproduction makes it possible to use the figures for direct measurement.

There are a series of reconstructions which will delight a reader bent on adding to his knowledge of anatomy: these present the planes of the sectioning with reference to 1) the cranial vault, sutures, brain, ventricles, mandible, and so on; 2) the midsagittal structures including the brain, brainstem, and cervical spinal cord; 3) the system of larger arteries; and 4) the system of larger veins.

The illustration of each section is preceded by a diagram in the sagittal plane indicating the exact level of the particular section. The total result of this care and attention is to facilitate a three dimensional conception.

The reviewer was amused at listing the number of pages; these are no index whatsoever to the amount of information given in the reproductions nor of the amount of anatomy that can be learned from studying them. The text is negligible. This is exact anatomic material set before one without the inconveniences of the dissecting room. It is learning by direct perception rather than by reading. To the neurologist and the neurosurgeon this classical anatomic treatise will be a source of frequent and accurate reference.

A. R. V.

Brain Tumors. Their Biology and Pathology

K. J. Zülch, M.D. Translated by Alan B. Rothballer, M.D. and Jerzy Olszewski, M.D., Ph.D. New York: Springer Publishing Company. 320 pages, $9.50.

SEVERAL DECADES have elapsed since any systematic treatise on the pathology of intracranial tumors as a whole has been published in the English language. Meanwhile, a huge literature on the subject has accumulated, so crowded with minutiae, with bewildering diversification of terminology, and often with controversy that there is presently a great need for a balanced and authoritative review of the whole topic. This is a need felt, especially by neurologists and neurosurgeons whose primary interest is in the application of pathologic information and principles to the clinic. It is to clinicians that the book is addressed, and they will find it an extraordinarily effective and satisfying answer to their requirements.

The work is solidly based on the author's own enormous pathologic experience with 4,000 brain tumors from the neurosurgical

clinic of Prof. Tönnis and is indeed a condensation of the writer's exhaustive treatment of this material in volume 3 of the *Handbuch der Neurochirugie* edited by Olivecrona and Tönnis. The precis has been done with such skill and discrimination that it presents the meat of the larger work without being in the least either superficial or crowded.

The first half of the book is devoted to a consideration of the general characteristics of brain tumors, including classification, structure, age and sex incidence, preferential localization, and mechanical displacement of the intracranial contents. All of these topics are discussed with an eye to their diagnostic and prognostic significance. The author's system of classification of the neuroepithelial tumors conforms in the main to that of Bailey and Cushing, based on histogenetic equivalents but with certain logical changes in grouping. But he insists upon the importance of avoiding too great a dependence upon the cell type for morphologic diagnosis and emphasizes an "organoid" approach, giving full consideration to the total architecture of the tumor and its manner of growth.

The remainder of the book is concerned with the gross and microscopic anatomy of the individual tumor types, illustrated in each instance by well chosen photographs of excellent technical quality. One wishes that the author's beautiful atlas of colored microphotography of brain tumors were more generally available, as it forms a most useful supplement to the present work. A well selected bibliography from the world literature completes the volume.

Dr. Rothballer and Dr. Olszewski are to be congratulated also for making the work available in such a clear and effortless translation.

R. B. R.

The Human Brain,
From Primitive to Modern

A. M. Lassek. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 242 pages, $4.75.

THIS TREATISE is an attempt to present a philosophy of man based on speculation concerning the nature and origin of the human nervous system. The author ventures quite boldly into the fields of cosmology and metaphysics and thereby invites disputation at almost every turn.

An interesting though brief historical account of the functions ascribed to the human brain and a graphic review of its growth and development are presented. The sketch of the anatomy may be too diffuse and could lead to misunderstanding; the general reader may need more definitions. The comparative anatomy and physiology of the brain are discussed at some length, with constant emphasis on theoretical considerations.

The chapter on "Evolution of the Mind" takes up two-thirds of the book and is at its best when describing structure, but at its weakest when, after amassing a superb amount of data on the wonder of man's achievements, the attempt is made to correlate them with anatomy. Evidence is offered for such correlation, but it emerges out of clinical observation and pathology and is perhaps too remote to attempt significantly to relate it to the observations and hypotheses of anthropologists.

The author does not provide for the development of the idea of psyche and uses the term simply as meaning a spirit which enters and leaves the body. The more subtle idea of psyche, that is, the totality of characteristics constituting a living man as compared with his dead counterpart, a principle of the whole of life phenomena and not merely of mind, is not mentioned or utilized by the author. As a result, comparisons of the asserted ignorance of the past with the enlightenment of the present take on an almost ludicrous contrast. Often the subject matter of the book, "The Human Brain," is lost in a cloud of folklore and primitive tribal customs. It appears likely that we have some years of patient measuring and observing to do before we may be able to correlate the patterns of the development of man as described by cultural anthropologists with the gross and microscopic anatomy of his brain.

A. R. V.

A Classification and Outline of Cerebrovascular Diseases

A report by an *ad hoc* Committee established by the Advisory Council for the National Institute of Neurological Diseases and Blindness, Public Health Service.

Foreword

Pearce Bailey, M.D.

CEREBROVASCULAR DISEASE is a major unsolved medical problem, the third ranking killer, and a foremost crippler of all diseases in the United States. In 1955, 175,120 persons in the United States died from cerebrovascular lesions. It is estimated that over one million Americans today are disabled because of this condition. Cerebrovascular death or disability can strike at any age but is more common past middle age.

Of the cerebrovascular deaths in 1955, 39,600 were in the working age group, 25 to 64 years. Yet, in spite of its scope as a public health problem, there is a remarkable void in our knowledge of the subject – and what research has been done in this field has been sporadic and scattered.

The attack on cerebrovascular disease concerns not only the neurologist and neurosurgeon, but also the general practitioner, the internist, the geriatrician, the physiatrist, the pediatrician, the psychiatrist, in fact, all clinicians. Also, on the basic science level it concerns the anatomist, pathologist, physiologist, biochemist, and psychologist. To meet such a multidisciplinary challenge, both clinical and basic, a pooling of multidisciplinary effort and talent into a cooperative research attack on the problem appears to be propitious.

Already two nationwide cooperative studies in specialized aspects of cerebrovascular disease have been initiated under the auspices of the National Institute of Neurological Diseases and Blindness. The first, a cooperative project designed to involve at least two dozen research medical centers, is aimed at the evaluation of treatment of subarachnoid hemorrhage and intracranial aneurysms; in the second, a number of research teams have joined forces to evaluate the use of anticoagulants, if any,

Director, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

for the prevention of cerebrovascular accidents.

Cooperative projects of this nature can be most advantageously activated, however, only if the present day criteria for the classification and diagnosis of cerebrovascular disease are more precisely and uniformly established.

With this point of departure, in June 1955 the National Advisory Council of the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, authorized the establishment of an *ad hoc* committee of experts on cerebrovascular diseases. They were asked to study the problem and develop uniform criteria for classification and diagnosis. These criteria, it was hoped, might be embodied into a scientific protocol for all cooperatve research projects in this field.

Since September 1955 this committee, under the chairmanship of Clark H. Millikan, has been working on this problem. The following pages reveal the efforts of their work, their preliminary criteria for the definition, classification, and general clinicopathologic aspects of cerebrovascular disease.

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*Introduction**

THE PURPOSE of this report is two-fold: first, to place in classified form all of the known types of cerebrovascular diseases, and second, to give meaning to such a classification by defining all terms used so clearly that they can be employed interchangeably by all investigators in various parts of the country. To achieve this goal, some discussion of morbid anatomy is necessary in certain instances in order to make specific words or phrases fully understandable, while in others a fairly detailed account of clinical manifestations seemed to be the only suitable method of making clear the definition of the terms used.

Our ultimate objectives are to obtain greater clarity of thinking in regard to cerebrovascular diseases, to compose a generally acceptable classification, to establish reliable criteria for diagnosis, and to promote further research in this field. During the first meeting of our committee, it became apparent that an acceptable classification and a set of uniform diagnostic criteria for each disease category were essential to the collective activities of the group. Without these preliminary steps, there could be no satisfactory means of further communication and no basis for comparison of groups of cases.

In this report we have endeavored to state certain aspects of cerebrovascular diseases which should be interpreted as a first attempt. Admittedly, many of the statements made on the following pages are only partially correct and, as our understanding of causes and mechanisms increases, they will surely undergo many changes.

*By Clark H. Millikan, M.D., consultant in neurology, Mayo Clinic, and chairman, NINDB *ad hoc* Committee on Cerebrovascular Diseases. In collaboration with committee members: Raymond D. Adams, M.D., chief of neurology services, Massachusetts General Hospital; Harry Fang, M.D., assistant professor of medicine (neurology), University of California Medical School; C. Miller Fisher, M.D., associate neurologist, Massachusetts General Hospital; Albert Heyman, M.D., associate professor of medicine, Duke University; Ellen McDevitt, M.D., assistant professor of medicine, Cornell University Medical College; A. L. Sahs, M.D., professor and head of neurology, State University of Iowa; and Peritz Schienberg, M.D., associate professor of neurology, University of Miami.

A DEFINITION OF CEREBROVASCULAR DISEASE

Since most diseases of the brain have a vascular aspect of some kind, it became necessary at the very outset to delimit the field of cerebrovascular disease. By the term "cerebrovascular" we denote all diseases in which one or more blood vessels of the brain are primarily involved in a pathologic process. Under pathologic process we would include an abnormality of the vascular wall, occlusion by thrombus or embolus, change in the caliber of lumen, and altered permeability to plasma and blood cells.

After some deliberation the term "cerebrovascular" was chosen to designate this whole category of diseases. It seems likely to find a general acceptance and already has the sanction of many contemporary writers. "Cerebrovascular" and "cerebral" are used in the original Latin sense, referring to the whole brain and not merely the hemispheres of the forebrain.

BASIS OF THE CLASSIFICATION

The basis of the classification is pathology, except in those groups of diseases where only the clinical features are known. Of the nine major categories, the three most important are cerebral infarction (I), transient focal cerebral ischemic attacks without infarction (II), and intracerebral hemorrhage (III). Since categories I and III are the main pathologic processes involving the brain parenchyma, nearly all vascular diseases will be found classified under one or other of these two headings. However, the nature of the pathologic process going on within the vessels forms a part of the diagnosis, as does the parenchymal change. Therefore, especially for the pathologists, it was necessary to add four separate categories, namely, vascular malformations and developmental abnormalities (IV), the arteritides (V), vascular diseases without changes in the brain (VI), and venous thrombosis (VIII). In certain instances, a disease had to be listed under more than one major category.

The intention throughout has been to make the classification as serviceable as possible to the clinician and to the pathologist, as well. In the interest of practicability and to assist the student, we have used bold-face type for the common diseases and italics for the less common ones or for those of lesser diagnostic importance.

A Classification and Outline of the Cerebrovascular Diseases

I. **CEREBRAL INFARCTION (PALE, RED [HEMORRHAGIC] AND MIXED TYPES (412)**

A. THROMBOSIS WITH ATHEROSCLEROSIS (412)

B. CEREBRAL EMBOLISM (414)

1. **Of cardiac origin**

a). **Atrial fibrillation and other arrhythmias (with rheumatic, atherosclerotic, hypertensive, congenital heart disease)**

b). **Myocardial infarction with mural thrombus**

c). **Acute and subacute bacterial endocarditis**

d). **Heart disease without arrhythmia or mural thrombus**

e). *Complications of cardiac surgery*

f). *Nonbacterial thrombotic ("marantic") endocardial vegetations*

g). *Paradoxical embolism with congenital heart disease*

2. **Of noncardiac origin**

a). **Atherosclerosis of aorta and carotid arteries (mural thrombus, atheromatous material)**

b). **From sites of cerebral artery thrombosis**

c). **Thrombus in pulmonary veins**

d). *Fat*

e). *Tumor*

f). *Air*

g). *Complications of neck and thoracic surgery*

h). *Miscellaneous: rare types*

i). *Of undetermined origin*

C. OTHER CONDITIONS CAUSING CEREBRAL INFARCTION (417)

1. **Cerebral venous thrombosis**
2. **Systemic hypotension**
3. **Complications of arteriography**
4. **Arteritis (see VI)**
5. **Hematologic disorders (polycythemia, sickle-cell disease, thrombotic thrombopenia, etc.)**
6. *Dissecting aortic aneurysm*
7. *Trauma to carotid*
8. *Anoxia*
9. *Radioactive or x-ray radiation*
10. *With tentorial, foramen magnum, and subfalcial herniations*
11. *Miscellaneous: rare types*

D. CEREBRAL INFARCTION OF UNDETERMINED CAUSE (418)

Continued

II. **TRANSIENT CEREBRAL ISCHEMIA WITHOUT INFARCTION (419)**

A. RECURRENT FOCAL CEREBRAL ISCHEMIC ATTACKS (419)
(Previously called vasospasm, usually associated with thrombosis and atherosclerosis)

B. SYSTEMIC HYPOTENSION ("simple faint," acute blood loss, myocardial infarction, Stokes-Adams syndrome, traumatic and surgical shock, sensitive carotid sinus, severe postural hypotension) (420)

1. **With focal neurologic deficit**

2. **With syncope**

C. MIGRAINE (421)

III. **INTRACRANIAL HEMORRHAGE (421)**
(Including intracerebral, subarachnoid, ventricular, rarely subdural)

A. HYPERTENSIVE INTRACEREBRAL HEMORRHAGE (421)

B. RUPTURED SACCULAR ANEURYSM (422)
(IF UNRUPTURED SEE IV A)

C. ANGIOMA (424) (IF UNRUPTURED SEE IV B)

D. TRAUMA (424)

E. HEMORRHAGIC DISORDERS (LEUKEMIA, APLASTIC ANEMIA, THROMBOPENIC PURPURA, LIVER DISEASE, COMPLICATION OF ANTICOAGULANT THERAPY, ETC.) (425)

F. OF UNDETERMINED CAUSE
(NORMAL BLOOD PRESSURE AND NO ANGIOMA)

G. *Hemorrhage into primary and secondary brain tumors*

H. *Septic embolism, mycotic aneurysm*

I. *With hemorrhagic infarction, arterial or venous (see under I and VII)*

J. *Secondary brainstem hemorrhage (temporal lobe herniation)*

K. *Hypertensive encephalopathy*

L. *Idiopathic brain purpura*

M. *With inflammatory disease of arteries and veins (see under VI, VII)*

N. *Miscellaneous: rare types*

Continued

IV. VASCULAR MALFORMATIONS AND DEVELOPMENTAL ABNORMALITIES (426)

A. ANEURYSM – SACCULAR, FUSIFORM, GLOBULAR, DIFFUSE (426) (if ruptured see III B)

B. ANGIOMA (including familial telangiectasis, trigeminal encephalo-angiomatosis (Sturge-Weber-Dimitri), retinal-pontine hemangiomas) (427) (if ruptured see III C)

C. ABSENCE, HYPOPLASIA, OR OTHER ABNORMALITY OF VESSELS (including variations in pattern of Circle of Willis) (427)

V. INFLAMMATORY DISEASES OF ARTERIES (427)

A. INFECTIONS AND INFESTATIONS (428)

1. **Meningovascular syphilis**
2. **Septic embolism**
3. *Arteritis secondary to pyogenic and tuberculous meningitis*
4. *Rare types (typhus, schistosomiasis mansoni, malaria, trichinosis, etc.)*

B. DISEASES OF UNDETERMINED ORIGIN (428)

1. *Lupus erythematosus*
2. *Rheumatic arteritis*
3. *Polyarteritis nodosa (necrotizing and granulomatous forms)*
4. *Cranial arteritis (temporal)*
5. *Idiopathic granulomatous arteritis of aorta and its major branches*

VI. VASCULAR DISEASES WITHOUT CHANGES IN THE BRAIN (429)

A. ATHEROSCLEROSIS

B. HYPERTENSIVE ARTERIO- AND ARTERIOLOSCLEROSIS

C. *Hyaline arterio- and arteriolosclerosis*

D. *Calcification and ferruginization of vessels*

E. *Capillary sclerosis, etc.*

VII. HYPERTENSIVE ENCEPHALOPATHY (430)

A. MALIGNANT HYPERTENSION (essential, chronic renal disease, pheochromocytoma, etc.)

B. ACUTE GLOMERULONEPHRITIS

C. ECLAMPSIA

Continued

VIII. DURAL SINUS AND CEREBRAL VENOUS THROMBOSIS (430)

- A. SECONDARY TO INFECTION OF EAR, PARANASAL SINUS, FACE, OR OTHER CRANIAL STRUCTURES
- B. WITH MENINGITIS AND SUBDURAL EMPYEMA
- C. *Debilitating states (marantic)*
- D. *Postpartum*
- E. *Postoperative*
- F. *Hematologic disease (polycythemia, sickle-cell disease)*
- G. *Cardiac failure and congestive heart disease*
- H. *Miscellaneous: rare types*
- I. *Of undetermined cause*

IX. STROKES OF UNDETERMINED ORIGIN (431)

A Classification and Outline of Cerebrovascular Diseases

VASCULAR DISEASES of the brain may be regarded as having three separate aspects: 1) The basic pathologic process which involves the vessel, that is, atherosclerosis, embolism, hypertensive change, malformation, "spasm," arteritis, and increased permeability to plasma and cells. As a result of these changes the blood vessel is either blocked or ruptures and, as in other organs, vascular disease can therefore be reduced to "plugs" and "leaks." 2) The pathologic changes wrought in the cerebral tissues by either occlusion of a vessel (infarction) or rupture of a vessel (hemorrhage). 3) The neurologic disturbances which result from infarction and hemorrhage. In a sense, these are the three dimensions of cerebrovascular disease. In considering the different types of cerebrovascular disease, we shall, in each instance, touch upon all three of these aspects.

THE MORBID ANATOMY

In order to determine the nature, cause, and pathogenesis of cerebrovascular diseases, three types of data are necessary: 1) an exact description of the primary blood vessel abnormality, as it exists during life and after death; 2) the cerebral tissue changes induced by these vascular abnormalities and the functional disorders resulting therefrom; and 3) the reactive and adaptive changes which delimit and repair the effects of the insult. Further data are needed on all of these points and only tentative statements can be made at this time.

It has been particularly difficult to achieve a precise definition of the primary vascular abnormalities. Some of the nutrient arteries of the brain are relatively inaccessible in the neck and base of the skull and are not examined routinely. The disease process may be so devastating that it destroys the vascular lesion and the vessel on which it lies, as sometimes happens in hypertensive hemorrhage. Furthermore, after studying the parenchymal lesion it is often difficult to determine the vascular disease because of disturbance of architecture resulting from the dissection. The usual pathologic technic of random sampling is unsuited to the elucidation of the vascular diseases of the brain. At present the principal diseases of the brain arteries may be listed as follows: atherosclerosis, hyaline arterio- and arteriolosclerosis, hyperplastic arterio- and arteriolosclerosis, necrotizing arteriolosclerosis, embolism, dissecting arterial aneurysm (Charcot-Bouchard miliary aneurysms), polyarteritis nodosa, and granulomatous arteritis and arteriolitis. Their causes, however, have yet to be ascertained. What little is known of their nature and mode of development will be presented in the sections which follow. The situation of the vascular lesion in the whole system of cerebral vessels must be determined and the availability of anastomotic pathways must be ascertained.

It is important for the clinician to keep in mind that the effect of vascular diseases on the brain can be reduced to two essential processes: 1) infarction and 2) hemorrhage. This formulation, although simple, is an accurate one. Apart from these, vascular disease evokes no important effect and is silent. The only exceptions to this statement are occasional instances of increased intracranial pressure (hypertensive encephalopathy and venous thrombosis), distortion of neighboring structures (aneurysm), and headache (hypertension, aneurysm and vascular malformation, migraine, cranial arteritis). Of course, the structural changes must be viewed in their relation to the major anatomic landmarks.

CEREBRAL INFARCTION

Brain tissue has no stored supply of oxygen and is dependent from minute-to-minute on an adequate flow of blood. When nervous tissue is deprived of oxygen for more than a

few minutes, as when its artery of supply is blocked by thrombus or embolus, the cells are irreversibly injured and their living-machinery is wrecked. The cells, both nerve and glia, disappear, nerve fibers degenerate, and the supporting tissues and smaller blood vessels are destroyed. The involved tissue becomes swollen and then disintegrates, a process which is called "softening." Over a period of weeks and months the necrotic debris is removed by macrophages, and then fibroblastic and astrocytic connective tissue proliferation forms a meshwork which knits up the defect. The process of softening due to ischemia is called *infarction;* the lesion is an *infarct.* Infarcts may be small (a few millimeters) or large (several centimeters), single or multiple, unilateral or bilateral, patchy or uniform, superficial or deep, and cortical or subcortical. The territory of any cerebral vessel can be affected.

Infarcts may be a) pale, b) red (hemorrhagic), or c) mixed. Disregarding the slight degree of congestion which can be seen in all softenings, the infarcted tissue, both cortex and white matter, is uniformly pallid in many cases and is classed as a *pale infarct.* In other instances, that part of the softening which involves gray matter is dotted with petechial hemorrhages, giving the infarct a distinctly red appearance; infarcts of this type are termed *red or hemorrhagic infarcts.* The explanation for these small extravasations within infarcted gray matter is not known, but in many cases cerebral embolism is responsible. At times the infarct is so uniformly red that, to the unpracticed eye, it appears to be a hemorrhage. In the most severe cases of this kind, blood may tinge the cerebrospinal fluid, but as a rule this does not occur in ordinary hemorrhagic infarction. It is not uncommon for infarcts to be partly pale and partly red, that is, *mixed.*

CEREBRAL HEMMORRHAGE

Hemorrhage results from rupture of a vessel, and the ensuing pathologic process does not differ from that following hemorrhage elsewhere in the body. Blood which has escaped into brain tissue is slowly removed over a period of months, partly by macrophages, partly by diffusion. Large hemorrhages usually stem from an artery; small extravasations commonly arise from veins and capillaries. Hemorrhage may occur from a large vessel or a very small one, and this is usually reflected in the speed of bleeding and also the size of the blood clot. There are several causes for leakage from a vessel – hypertension, aneurysmal dilatation, hemorrhagic blood diseases, and so on. It is damage to neighboring vital centers which makes brain hemorrhage such a grave illness.

Lastly, if the study of the neurovascular process is to be complete, and if an exact temporal correlation of clinical and pathologic events is to be made, the stage of the various adaptive and reparative processes within the nervous tissue and vessels must be determined. Among the many questions to be answered are: What is the age of the infarct or hemorrhage? If there is more than one lesion, are all of the same age or not? Is the vascular occlusion recent or old? Do the elements of the occluding mass indicate formation in situ (thrombus), or an origin elsewhere (embolus)?

Since strokes are associated with either infarction or hemorrhage, and since infarction is usually the result of thrombosis or embolism, it can be deduced that three basic processes account for almost all strokes, namely, thrombosis, embolism, and hemorrhage. The only common exceptions to the rule are recurrent ischemic attacks, hypertensive encephalopathy, migrainous hemiplegia, and syncope.

THE CEREBROVASCULAR STROKE AS A CLINICAL PHENOMENON

Clinically, the common denominator of all forms of vascular disease of the brain is a "stroke." This term is commonly used colloquially and by physicians, along with the term "shock."* Reduced to the simplest terms, a cerebrovascular stroke may be defined as a focal neurologic disorder of abrupt development due to a pathologic process in blood vessels. In addition to its focal character, the most essential feature is its *temporal profile*

*There is no satisfactory word for this condition in the English language. Apoplexy, meaning "to be struck down," is too strong, for all forms of cerebrovascular disease do not fell the patient. Furthermore, it has no adequate nominal form. One cannot say, "the patient had an apoplexy." "Shock," "stroke," and "accident" all have several other meanings. When they are used one should, in order to be specific, speak of a cerebrovascular stroke, cerebrovascular shock, or cerebrovascular accident.

which is characterized by abrupt onset and rapid evolution, the symptoms usually reaching a peak of severity in seconds, minutes, or hours; if not at once fatal, a partial or complete recovery usually occurs in a period of hours, days, weeks, or months. A relentless, downhill course over a period of days, weeks, or months with steadily increasing neurologic impairment is usually not a mark of cerebrovascular disease. However, at times this type of clinical course may be most difficult to distinguish from the saltatory progression of symptoms which occurs in some cases of thrombotic vascular disease. The accretions of neurologic derangement in the latter condition may be so slowly cumulative that only a careful history will bring out the fact that the disease has advanced by a series of small strokes, often with some improvement between attacks. Without the identifying characteristics of the stroke, the clinical diagnosis of cerebrovascular disease is always uncertain.

There are remarkably wide variations in the pattern and severity of strokes. They may take the form of a violent assault in which the patient falls in his tracks deprived of sense and motion and lies like a person in deep sleep, with face flushed, breathing stertorous or in the waxing, waning rhythm of Cheyne-Stokes, and the pulse full and slow. One arm and leg are flaccid as a rule. Death usually occurs in a few hours or days, seldom during the first seconds or minutes of the attack, as in cardiac and pulmonary disease. On the other hand, a stroke may consist only of some slight deficit or derangement of speech, thought, voluntary motion, somatic sensation, or vision. Consciousness is not abolished and often not even altered. Symptoms may last for a period varying from seconds to minutes or longer, or they may persist indefinitely. Some degree of recovery is almost invariable. This is by far the most frequent type of cerebrovascular stroke. Between these two extremes, there are innumerable forms which a stroke may take.

The number and variety of neurologic symptoms are almost unlimited, and their recognition requires a knowledge of neurology. Certainly the most common sign in all forms of stroke is a hemiplegia due to involvement of the motor part of one cerebral hemisphere or the corticospinal tract. However, other focal neurologic manifestations such as homonymous hemianopia, monocular or binocular blindness, aphasia, hemihypesthesia, rotational dizziness, quadriplegia, dysphagia, or slurred speech may also occur. It is in the slight cerebrovascular stroke or in the early stages of the development of a more severe one that a paralysis of one side of the body is apt to be absent.

In addition to the focal neurologic deficit, there may also be a more diffuse or general disturbance of brain function. The latter condition is manifested by drowsiness, confusion, stupor, coma, ipsilateral random movements, grasp reflex, and Babinski sign — symptoms and signs which, under the circumstances, cannot be ascribed to a particular anatomic region of the brain. These more diffuse cerebral symptoms, prominent in lesions which are sudden and extensive, as in hemorrhage or massive infarction, are variously attributed to diaschisis or general cerebral shock, to increased intracranial pressure, to temporal lobe herniation, and to midbrain compression. They are nearly always transitory, usually being more regularly reversible than the focal symptoms and signs.

While some combinations of signs are almost specific indicators of a cerebrovascular stroke, the diagnosis is usually based on the entire constellation of clinical features. Often the patient is elderly and arterial hypertension or diabetes is present. There may be evidence of vascular disease at other sites, for example, heart, lower limbs, and aorta. A source of emboli may be evident (auricular fibrillation, myocardial infarction, subacute bacterial endocarditis, and so on). Many strokes are preceded by transient warning episodes of weakness or numbness which, if they are nonconvulsive in nature, should always suggest the diagnosis of cerebrovascular disease. Certain combinations of neurologic signs, for example, those which accompany a lateral medullary lesion, are of themselves so characteristic as to be recognized as of vascular origin. Lastly, in intracranial hemorrhage the presence of blood in the cerebrospinal fluid immediately stamps the process as vascular, provided brain trauma is excluded, and diagnostic deductions can proceed from that vantage point.

The distinction between a vascular process and other types of neurologic illness, such as tumor, abscess, demyelinating disease, and subdural hematoma, is not always easy to make. In their more advanced clinical stages, many of these diseases come to resemble the patterns of vascular disease. It is then that a return to first clinical principles, a careful history of the evolution of symptoms, and an evaluation of all elements of the total syndrome have prime importance. An accurate symptom-by-symptom reconstruction of the timetable of development of the illness is indispensable for the diagnosis of cerebrovascular disease, just as it is throughout the entire field of medicine.

THE PRINCIPAL TYPES OF CEREBROVASCULAR DISEASE

I. CEREBRAL INFARCTION

A. THROMBOSIS WITH ATHEROSCLEROSIS

This combination is the most common cause of strokes, accounting for approximately 50 per cent of all cases. Athertosclerosis is the primary disease, and thrombosis is added at a relatively late stage.

Atherosclerosis is that type of arteriosclerosis in which lipid material accumulates subintimally. Its formation and properties in brain arteries do not differ from the disease in other parts of the body. It tends to form at bifurcations, branchings, and curves. Hypertension clearly aggravates the process and leads to lipid deposition in smaller vessels, such as the penetrating arteries, cerebellar arteries, and others. In general, its severity in brain arteries parallels that in vessels elsewhere, for example, in aorta, lower limbs, and heart. While most common in the elderly, it may be severe in the fourth and fifth decades. The carotid and basilar systems are equally affected. Sites of predilection include the internal carotid artery at the carotid sinus and at the clinoid process, the first major bifurcation of the middle cerebral artery, the anterior cerebral artery at its origin and as it curves around the genu of the corpus callosum, the vertebral arteries near their junction to form the basilar artery, the lower first centimeter of the basilar artery, the upper bifurcation of the basilar artery, and the posterior cerebral artery as it winds around the cerebral peduncle. Occlusion is more frequent at these sites than elsewhere.

As the atherosclerotic plaque thickens, the vascular lumen narrows, and blood flow is diminished and its margin of safety reduced. It is remarkable how severe atherosclerosis may be in the cerebral arteries without giving rise to clinical manifestations or to pathologic changes in brain tissue. Only with the advent of thrombosis resulting in complete occlusion of the lumen, or when the systemic blood pressure falls to a level which is insufficient to force blood in the required amount past the atherosclerotic "narrows," does cerebral ischemia occur. It is relatively uncommon for atherosclerosis itself to block vessels completely and, for the most part, vascular occlusion is a combination of *atherosclerosis plus thrombosis*.

The mechanism by which thrombus is precipitated upon a plaque is poorly understood. Suggested hypotheses include ulceration of the plaque, hemorrhage into the plaque, edema of the plaque, slowing of the blood stream, and eddying. Hypercoagulability of the blood has been suspected, but no technic has so far been able to measure such an abnormality. The possible importance of this factor is indicated by the finding at pathologic examination that in some cases atherosclerosis is widespread in cerebral arteries, yet no thrombotic occlusion has occurred, and in other cases atherosclerosis is scanty but thrombus has been deposited in association with each plaque. The speed with which thrombus builds up, whether it takes minutes, days, or weeks to produce occlusion, is not known. No doubt it differs from case to case. In addition to the primary deposition of thrombus upon a plaque, a secondary clot may spread distally and proximally.

The exact result of a vascular occlusion is not always easy to predict. Depending on the availability of collateral blood flow via the circle of Willis or subarachnoid interarterial anastomoses and on the maintenance of the systemic blood pressure, the spectrum of change is highly variable. At one extreme the entire territory of an artery distal to the site of the occlusion may be severely infarcted; on the other hand, collateral flow may be sufficiently abundant to supply the impoverished

tissue so that no infarction whatsoever will result. Between these two extremes the infarct may take countless forms, depending again on local and general factors. Since the speed of thrombosis is unknown and the effect of occlusion is rather unpredictable, the temporal correlation of vascular and clinical events remains unsatisfactory at present.

The Clinical Picture

Usually the stroke *develops abruptly*, often coming on during *sleep* or within *an hour of arising*. The neurologic deficit may be maximal when first discovered or may require several hours or even a day or so to evolve. In a high percentage of cases there will have been *transient warning symptoms* borrowed from the clinical picture which is finally to develop. Often the full blown stroke does not develop as a single attack but comes on over a period of days or weeks in the form of abrupt worsenings, until finally the complete picture for that particular type of stroke has accumulated. Temporary improvement may occur between episodes of worsening. The patient, although usually elderly and hypertensive, is not invariably so, and normotensive patients in the fourth decade may be stricken. Diabetes aggravating the underlying atherosclerosis is not uncommon. In many cases there will be evidence of vascular disease elsewhere, for example, myocardial infarction, electrocardiographic changes, absence of peripheral pulses in the lower limbs (dorsal pedal, posterior tibial, popliteal, or femoral).

Since most of the vessels are inaccessible within the skull, the diagnosis of cerebral thrombosis is made largely by inference from the neurologic picture. In carotid occlusion, however, loss of pulsation in the internal carotid artery in the neck and pharynx, decrease of the ipsilateral central retinal artery pressure, and the presence of a contralateral intracranial bruit provide more specific indications of the site of the trouble.

Headache is not uncommon in the early stages of a thrombotic stroke and its location may assist in accurate diagnosis. The *cerebrospinal fluid* in cerebral thrombosis with atherosclerosis is normal in the great majority of cases, but occasionally there will be increased protein (usually less than 100 mg. per cent) and rarely the leukocytes in the spinal fluid will number several hundred per cubic millimeter. In the presence of extensive infarction, the cerebrospinal fluid pressure may be elevated and papilledema may appear.

Syndromes of the Cerebral Arteries

The details of the neurologic picture depend primarily, of course, on which vessel is occluded and where the infarct lies. In the following paragraphs a brief outline of the principal features associated with each of the cerebral arteries is presented. These clinical data are applicable to both thrombotic and embolic cerebrovascular disease. It must be understood that partial syndromes and minor variations are extremely common; indeed, they are in the majority.

Middle cerebral artery. The characteristic findings are a contralateral hemiplegia, cortical sensory deficit (cortical hypesthesia), and hemianopsia. If the occlusion is on the dominant side of the brain, aphasia will be added; on the nondominant side, agnosias of the minor hemisphere are noted. If the infarct is massive in this or any of the cerebral arteries, stupor may occur. In the middle cerebral territory, the motor and sensory cortical areas representing different parts of the body occupy a large territory and hence an infarct may produce paralysis of the face alone, of only one limb, or even part of one limb; this restricted deficit is referred to as monoplegia. If the infarct lies posteriorly in the middle cerebral territory, hemianopsia, dysphasia, or agnosia will occur alone or will dominate the clinical picture; if the infarct lies centrally in the motor-sensory strip, a hemiplegia with sensory change will be the chief finding, and if further anteriorly, paralysis, often monoplegic without a sensory deficit, will predominate.

When the deep territory of the middle cerebral artery is involved, that is, the upper part of the posterior limb of the internal capsule and the adjacent basal ganglia, a global hemiplegia usually results, with face, arm, and leg affected together rather than in monoplegic form. This is due to the fact that the motor fibers lie closely packed in the capsule and, therefore, the fibers to only one limb are less likely to be singled out for destruction than in the cortex where the motor area covers an ex-

tensive territory. Damage to the basal ganglia produces no specific effects which have so far been recognized.

Anterior cerebral artery. The syndrome for this artery has not been clearly determined as yet, but the following manifestations are regarded as typical: paralysis and cortical hypesthesia of the opposite lower limb and possibly mild involvement of the opposite arm, as well; mental change, often described as dementia; apraxia of the left upper extremity; grasping and sucking reflexes; and incontinence of bowel and bladder (frontal lobe incontinence).

Posterior cerebral artery. As in the case of the other cerebral arteries, the syndrome depends on where in its course the artery is blocked. When only the superficial territory is involved, that is, the hippocampotemporo-occipital region, a hemianopsia results; in the case of the dominant hemisphere, alexia and mental change (often temporary) are added. If the occlusion interrupts the supply to the deeper structures in the thalamus and brainstem, there may appear a mild contralateral hemiparesis (cerebral peduncle), thalamic syndrome (posterior thalamus), contralateral cerebellar ataxia (superior cerebellar peduncle), and third nerve palsy. Bilateral posterior cerebral involvement in which both occipital lobes are affected results in cortical blindness; the patient is often unaware that he cannot see.

Internal carotid artery. Occlusion results most often in infarction of the middle cerebral territory, either total or partial. In this case the clinical picture will be the same as outlined for the middle cerebral artery. At other times, depending on the adequacy of anastomotic vessels in the circle of Willis, the anterior cerebral territory on one or both sides may also be involved and even the posterior cerebral territory. A telltale sign of occlusion of the internal carotid artery is monocular blindness, fleeting or permanent, involving the eye contralateral to the hemiplegia. This indicates interference with blood flow in the ophthalmic artery which arises from the internal carotid.

Vertebral artery. Usually there are two good-sized vertebral arteries, in which case unilateral occlusion of one is either silent or results in the lateral medullary syndrome (syndrome of the posterior inferior cerebellar artery) characterized by facial pain, rotational vertigo, vomiting, dysphagia, ipsilateral cerebellar ataxia and Horner's syndrome, contralateral loss of sensation for pain and temperature on the extremities and trunk, and homolateral involvement of these senses on the face. In other cases, cerebellar ataxia is the only sign developing as the result of damage to the inferior surface of the cerebellum. When there is but one good-sized vertebral artery and it becomes occluded, or when the artery on the opposite side has been previously thrombosed, occlusion of the remaining artery will produce the basilar artery syndrome, to which there may or may not be added the lateral medullary syndrome.

Basilar artery. This artery not only supplies the pons but usually the territory of the posterior cerebral arteries, too, including midbrain, thalamus, and the temporooccipital portion of the cerebral hemisphere. The hallmark of brainstem involvement is bilateral pyramidal tract signs, combined with unilateral or bilateral cranial nerve (III to XI) palsies. The clinical picture may include weakness or paralysis of all four limbs, with increased tendon reflexes and bilateral Babinski signs, dysphagia, dysarthria, diplopia, numbness of the face, weakness of a masseter muscle, stupor or coma, and rarely unilateral or bilateral deafness. To this basic picture there frequently are added rotational vertigo, cerebellar ataxia, long tract sensory deficit (spinothalamic or medial lemniscus), and visual field defects or blindness (calcarine cortex).

Anterior choroidal artery. Discussion of this artery has been omitted because of the present uncertainty surrounding its syndrome. Surgical ligation of the vessel often fails to elicit any recognizable neurologic deficit.

B. CEREBRAL EMBOLISM

In most cases of cerebral embolism, the embolic material is a fragment of thrombus or clot which has broken away from a thrombus within the heart. Embolism due to fat, tumor cells, or air is a rare occurrence and seldom figures in the differential diagnosis of strokes.

The embolus, carried swiftly along in the blood stream, is usually arrested at a bifurcation or other site of narrowing of the lumen. Ischemic infarction usually follows and is pale,

red, or mixed. It has already been pointed out that hemorrhagic infarction is particularly likely to be the result of embolism. Because of the speed with which occlusion occurs, there usually is not time for collateral influx to become established, and sparing of territory distal to the site of occlusion is not as common as in thrombosis. No region of the brain is immune from insult, but the territory of the middle cerebral artery is most frequently involved. Each of the hemispheres may be equally subject to occlusion. Large embolic masses block larger vessels (sometimes the carotids in the neck), while tiny fragments may reach vessels as small as 0.2 mm. and the resultant infarct might easily be overlooked at autopsy. The details of the behavior of embolic material are not fully known. Although often, perhaps in most cases, it remains arrested and plugs the lumen solidly, there is evidence that in many instances the embolus breaks up into fragments which enter smaller vessels or even disappear completely so that a careful examination fails to reveal their final location. The pathologic diagnosis must then be made by inference, for example, the absence of a vascular occlusion at the proper site to explain the infarct, a ready source of the embolus, infarcts in other organs such as kidney and spleen, the absence of atherosclerosis or other cause for thrombosis in the cerebral vessels, the presence of hemorrhagic infarction, and, last but not least, the clinical history. Almost every kind of heart disease can be associated with embolism. The commonest direct cause is *chronic atrial fibrillation* due to atherosclerotic or rheumatic heart disease. The source of the embolus is mural thrombus which is laid down in the auricular appendage. The mechanism of this deposition is not known. Noncontraction of the atrium, with resultant stagnation within the appendage, probably is a major factor, but the explanation for the occurrence of thrombus in one patient with fibrillation and not in another is still lacking. Atrial fibrillation due to other types of heart disease can, of course, also lead to embolism (hypertensive, congenital, thyrotoxic, syphilitic, and the like). Embolism probably occurs also during *paroxysmal auricular fibrillation or flutter*, but there is need for further exact documentation of such cases.

Mural thrombus deposited on the damaged endocardium overlying a *myocardial infarct* is the second most frequent source of cerebral emboli. At autopsy minor fragments of mural thrombus are often overlooked as they lie partly obscured by the trabeculae carnae and papillary muscles. Emboli can also arise from atrial thrombus due to *severe mitral stenosis* without atrial fibrillation. In recent years a new factor in the causation of cerebral embolism has been introduced, namely *cardiac surgery*. The performance of valvuloplasty and amputation of the auricular appendage in cases of rheumatic heart disease has been particularly prone to result in the dissemination of thrombus material, often with disastrous consequences. Emboli are said to arise in the dilated heart of congestive heart failure, but this matter needs to be inquired into further. *Subendocardial fibroelastosis* and *cardiac tumors* are rare causes of cerebral embolism.

The *vegetations of acute and subacute bacterial endocarditis*, being infected, give rise to septic embolism which may produce several different pathologic pictures in the brain. In some cases the infarcts (they are usually multiple) may not differ from those due to noninfected emboli, but in others there result small *septic infarcts* or miliary abscesses into which hemorrhage may occur. Another complication of septic embolism is mycotic aneurysm, now seen infrequently. This may be a source of cerebral or of subarachnoid hemorrhage. *Nonbacterial endocarditis*, also called "marantic" endocarditis, occasionally causes cerebral embolism and is capable of producing a most baffling clinical picture. *Paradoxical embolism* can occur when, due to congenital malformation of the heart, an abnormal communication exists between the right and left sides of the heart or both ventricles communicate with the aorta. Embolic material arising in the veins of the lower extremity or, indeed, anywhere in the systemic venous tree may then reach the cerebral circulation by bypassing the pulmonary circulation.

Emboli can also break away from mural thrombus deposited upon ulcerated atheroma in the arch of the aorta or in the carotid arteries. A heavy deposition of atheroma is frequently present in the carotid sinus and, if mural thrombus is deposited thereon, massage

of the sinus region in testing its sensitivity may dislodge material and produce a hemiplegia. Carotid massage must always be carried out gently. Occasionally *atheromatous material* extruded from a large plaque enters the blood stream and is swept along to lodge in distal vessels; fatty materials consisting of cholesterol clefts can be found within the embolus. Another related type of embolism, possibly of clinical importance, occurs when thrombus material which is building up at the site of incipient cerebral thrombosis is carried away before complete occlusion has occurred, leading to embolic obstruction of a distal branch. The pathologic picture then presents both thrombotic and embolic aspects.

The pulmonary veins, being on the systemic arterial side of the heart, may be a source of thrombotic material which passes through the left side of the heart to reach the brain directly. This route is plainly exemplified by cerebral abscess complicating pulmonary suppuration. Embolism may also follow lobectomy and pneumonectomy for carcinoma and chronic inflammatory diseases of the lung. It is always difficult to prove that an embolus had its origin in the pulmonary veins, since it is an arduous task to examine all pulmonary veins at autopsy; furthermore, if the entire clot were carried away, there would be no remnant left to indicate its source. Occasionally, *surgery of the neck and thorax* is followed by cerebral embolism, and with the increasing frequency of vascular surgery in these regions, an increase in the number of such complications can be expected. A rare type is that which follows thyroidectomy. Thrombosis in the stump of the superior thyroid artery extends proximally until a section of it protrudes into the lumen of the carotid and is carried away in the cerebral blood stream.

Cerebral fat embolism is closely linked to trauma and rarely enters into the stroke problem. Cerebral air embolism is a rare complication of pneumothorax therapy and of criminal abortion in pregnancy. Decompression sickness, another source of intravascular air bubbles, may also affect the nervous system but is not likely to simulate vascular disease. *Cerebral tumor embolism* must occur in each case in which secondary tumor is deposited within the brain, but rarely is the embolic tumor mass large enough to occlude a cerebral artery and produce the picture of a stroke.

Cerebral Emboli of Undetermined Origin

Not infrequently at autopsy, the diagnosis of cerebral embolism is made with full justification without finding a source. The same is true of embolism elsewhere in the body. Possibly the search for a thrombotic nidus has not been sufficiently thorough and obscure sources have been overlooked, as in the auricular appendage, among the papillary muscles, or in the pulmonary veins. Nevertheless, in some cases which have been studied very carefully, no source of embolic material has been discovered.

The Clinical Picture of Cerebral Embolism

Of all strokes, those due to cerebral embolism come on most rapidly, and the full blown clinical picture develops within several seconds or a minute. As a rule, there are no warning episodes whatsoever, but occasionally in embolic occlusion of the internal carotid artery proximal to the circle of Willis, a transient episode may precede the final arrival of the stroke. The embolus strikes at any time of the day or night, and if the stroke develops during sleep, its exact mode of development will not be known. The neurologic picture will depend on which artery is blocked and where along its course the obstruction lies. The syndromes for each cerebral artery which were outlined under thrombosis apply also in embolism. The cerebrospinal fluid is usually clear, under normal pressure, and contains either no cells or a few white cells. This is usually true even when the infarct is hemorrhagic, although slight xanthochromia may then appear and occasionally the number of red cells in the spinal fluid may rise as high as 5,000 per cu. mm. It must be emphasized that this is quite rare, and blood in the cerebrospinal fluid must be attributed to embolism only if supported by incontrovertible collateral evidence.

Although the abruptness with which the stroke develops and the lack of warning symptoms point to embolism, it is the total clinical picture upon which the diagnosis is based. If hemorrhage is ruled out, there remains only thrombosis to be excluded. A stroke in a young

person with rheumatic heart disease and auricular fibrillation presents no problem in diagnosis, provided a vascular malformation and nonvascular lesions such as multiple sclerosis and abscess can be ruled out. At any age a rapidly developing stroke in association with *auricular fibrillation* must be attributed to embolism until disproved. A history of embolism to other regions of the body provides additional evidence that the same process underlies the neurologic event.

The possibility that myocardial infarction with mural thrombus is responsible for the stroke must always be kept in mind; not infrequently, the first evidence of an otherwise silent myocardial infarct is the occurrence of embolism. Therefore, it is advised that an electrocardiogram be made in all cerbrovascular stroke cases of uncertain origin. Rare types of heart disease as a source of embolism, such as subendocardial fibroelastosis and cardiac tumor, need only be mentioned in passing. *Acute and subacute bacterial endocarditis* do not usually present as a stroke, although this does happen in a small proportion of cases and one must be alert to the possibility. In addition to the clinical signs of endocarditis, the presence of fever, cardiac murmurs, splenomegaly, and petechiae, and the discovery of pleocytosis in the cerebrospinal fluid will point to the correct diagnosis. The possibility of *nonbacterial endocarditis* (marantic) should always be entertained in cancer cases in which a stroke occurs. However, it may occur in association with other diseases such as lupus erythematosus (the verrucous endocarditis of Libman-Sacks) and in other of the "collagen diseases." Otherwise it can only be suspected in cases of repeated embolism in which other causes have been ruled out. Paradoxical embolism need be considered, of course, only in congenital heart disease and the diagnosis will usually not be difficult. However, if a patent foramen ovale is the only malformation, there may be no clue to its presence. To make the diagnosis of paradoxical embolism in the absence of evidence of frank septal defect is foolhardy.

The remaining causes of cerebral embolism, including cardiac surgery, neck surgery, pulmonary vein thrombosis, fat, air, and tumor, need not be expanded upon here.

C. OTHER CONDITIONS CAUSING CEREBRAL INFARCTION

This group includes nine unrelated, rather uncommon conditions which, when added to cerebral thrombosis with atherosclerosis and cerebral embolism, complete the list of the known causes of cerebral infarction. In *cerebral venous thrombosis* the venous circulation is obstructed, resulting in stagnation of blood flow, local anoxia, and infarction. This is discussed in section VII. In *cerebral arteritis*, whether syphilitic, tuberculous, or of undetermined nature, the vascular inflammation induces thrombosis and occlusion of the vascular lumen with resulting infarction of brain tissue. The arteritides are considered at greater length in section VI.

Since the systemic blood pressure is of major importance in determining cerebral blood flow, it is obvious that *systemic hypotension*, if sufficiently severe and prolonged, can precipitate cerebral ischemia and infarction. The commonest causes of systemic hypotension are "simple fainting," acute blood loss, acute myocardial infarction, Stokes-Adams syndrome, traumatic and surgical shock, carotid sinus sensitivity, cardiac arrest or anesthetic accident during surgery, and severe postural hypotension (idiopathic, postoperative, induced by autonomic blocking agents or reserpine, post-sympathectomy, diabetic, tabetic, and so on). When the cerebral arterial tree is healthy, severe hypotension usually causes diffuse widespread ischemic damage to the brain, but in some instances focal infarcts limited to specific arterial territories occur, possibly because of a preexisting reduced margin of safety in blood flow traceable to the pattern of the circle of Willis and the arrangement of anastomosing arteries. When the cerebral arteries are diseased and their lumen narrowed by atherosclerosis, upon which thrombus may be deposited, a precipitous fall in the systemic blood pressure may further reduce the blood flow through the narrowed vessels to such a degree that local ischemia takes place in the brain tissue distal to the site of the previously tolerated obstruction. If the blood pressure is promptly restored, the neurologic manifestations (hemiplegia, numbness, hemianopia, and so on) may be quickly reversed. This series of events is listed under section II B, *Tran-*

sient Cerebral Ischemia Without Infarction. Unfortunately, restoration of adequate blood flow is not always achieved in time and a more or less permanent neurologic deficit remains. This is by no means a rare occurrence. It is important to recognize and remedy the situation immediately, or better still, to prevent it. The blood pressure must be carefully maintained during surgical procedures in the elderly. Strokes frequently develop when older patients get out of bed postoperatively for the first time. A history of fleeting episodes of weakness or numbness prior to projected surgery indicates that a stroke may be imminent, in which case operation should be delayed if possible. Since the arterial obstruction which acts in conjunction with hypotension to produce local ischemia is usually due to atherosclerosis, this group should be regarded as closely allied to cerebral thrombosis with atherosclerosis.

Carotid and vertebral angiography has often been followed in the past by hemiplegia and visual disturbances, respectively, fortunately transient in the great majority of cases. These complications, which are much less common in recent years, are frequenetly attributed to vasospasm induced by the contrast medium but this explanation cannot be accepted without further proof.

Hematologic disorders, including polycythemia, sickle-cell disease, and thrombotic thrombopenia, are at times associated with thrombosis of the cerebral arteries. In polycythemia, pathologic studies have usually shown that thrombosis had occurred within atherosclerotic arteries, but a few cases of venous thrombosis are also on record. In sickle-cell disease the vascular pathology is far from clear. Again venous thrombosis had been found in some cases. Thrombopenia usually produces a hemorrhagic tendency, but in thrombotic thrombopenia the small cerebral vessels are occluded by platelet masses. The picture is not likely to simulate a stroke. A *dissecting aortic aneurysm* may occasion blockage of the innominate or left carotid arteries leading to unilateral or bilateral cerebral ischemia and infarction. *Trauma to the carotid arteries* after head injury, missile wounds of the neck, or a misplaced throat clamp during tonsillectomy may result in occlusion of the internal carotid artery and the picture of a stroke. *Anoxia,* as in carbon monoxide asphyxia or choking, usually causes diffuse neuronal damage of the brain, with the cerebral cortex, cerebellum, or hippocampus predominantly affected. However, in some cases local areas of infarction may be found, as exemplified in the well-known softening of the globus pallidus bilaterally. It is not to be anticipated that anoxemia will often produce the classic picture of a stroke. Finally, for the sake of completeness, the effect of *radioactive or x-ray emanation* on blood vessels is mentioned. Arteries are one of the tissues most susceptible to radiation damage, and the ensuing arterial necrosis is probably the direct cause of delayed degeneration of brain tissue which sometimes takes place after roentgen therapy of intracranial and extracranial tumors. In all probability this condition will never mimic a stroke, however.

D. CEREBRAL INFARCTION OF UNDETERMINED CAUSE

This category has been included chiefly for the pathologist. At postmortem examination one often finds old cerebral infarcts whose cause cannot be determined pathologically because of the lapse of time. In long-standing arterial occlusion it is often impossible to distinguish atherosclerosis with thrombosis from atherosclerosis with embolism or, indeed, from embolism alone. The clinical history in the case may be inadequate, inaccurate, or even lacking, offering no help in reconstructing the events surrounding the onset of the stroke (hypertension, acute myocardial disease, trauma, infection, and so on). Another reason why an infarct may remain unexplained lies in failure to examine the internal carotid arteries proximal to the clinoid processes or in the neck. Occlusion here may be overlooked, if only the vessels attached to the brain after its removal from the skull are examined. Furthermore, as previously stated, emboli break up and disappear, leaving behind an infarct but no trace of the embolic material. For these reasons and many more, the pathologist is often forced to make the diagnosis of *cerebral infarction of undetermined type.*

It is a common experience clinically to encounter stroke cases in which, despite me-

ticulous study, an accurate diagnosis of the type of underlying vascular disease cannot be achieved. The absence of blood from the cerebrospinal fluid may point strongly to infarction as the lesion rather than hemorrhage, but, as will be pointed out later, extravasated blood does not reach the subarachnoid space in all cases of intracerebral hemorrhage. Therefore, for such cases it is preferable to use section VIII, *Strokes of Undetermined Origin,* unless inspection of the brain through a craniotomy or burr hole has revealed an infarct or there is incontrovertible clinical evidence in favor of infarction (for example, repeated warning attacks or a typical lateral medullary syndrome).

In most cerebrovascular strokes due to infarction, the clinical diagnosis is made by inference only; therefore, in investigations of cerebrovascular disease, whether therapeutic or clinical, our bedside impressions must be corroborated by meticulous postmortem examinations. Many errors in judging the efficacy or therapy are traceable to incomplete pathologic studies.

II. TRANSIENT CEREBRAL ISCHEMIA WITHOUT INFARCTION

The inclusion of migraine and simple syncope in this group seems scarcely justified at first glance. However, they find a place here not only because they are good examples of cerebral ischemia and should be included for the sake of completeness, but also because each of them not infrequently enters into the differential diagnosis of cerebrovascular conditions. Attacks of faintness, weakness, "falling," or loss of consciousness are common in the elderly, and the question often arises as to the relation of these to incipient vascular disease, especially of the basilar system.

A. RECURRENT FOCAL CEREBRAL ISCHEMIC ATTACKS (previously called cerebral vasospasm)

The type of disorder referred to here occurs most typically in the form of warning attacks or premonitory transient manifestations which often herald the onset of a more severe cerebrovascular stroke. However, such episodes do not precede all kinds of strokes, and observation has shown that they are chiefly related to *cerebral thrombosis,* being virtually unknown in cases of intracerebral hemorrhage and rare before the onset of embolic infarction. In recent years increasing attention has been directed to these attacks, with the purpose in mind of preventing the arrival of the threatening stroke by administering anticoagulants at the stage of warning symptoms. Since therapeutic efforts initiated after infarction has occurred are usually unavailing, prevention is a logical aim. Thus, the recognition and correct interpretation of these forerunners may be of great practical importance.

There would seem to be no doubt that the attacks arise on the basis of a temporary ischemia and are due to a transient failure of the circulation locally. The symptoms and signs which characterize the episode vary from case to case, depending chiefly on which artery is affected. However, in any one case successive attacks are of approximately the same pattern. These cerebral ischemic attacks commonly indicate the final picture which the threatening stroke will take, if it does finally occur. The principal manifestations from the territory of each of the major arteries are as follows: the *middle cerebral* – contralateral mono- or hemiparesis, numbness, tingling, dysphasia, homonymous hemianopia, or scintillating scotomata: the *anterior cerebral*—weakness or numbness of the opposite leg, reflex incontinence, perhaps confusion; the *posterior cerebral*—hemianopia, scintillating scotomata, and, if there is bilateral involvement, temporary blindness; the *internal carotid* – contralateral weakness, numbness, or dysphasia as in middle cerebral disease; in addition, transient blindness or amblyopia of the eye on the side of the occluded vessel occurs in a minority of cases; the *vertebral basilar* – dizziness, monoparesis, hemiparesis or quadriparesis, numbness involving both sides of the body, staggering, ataxia, diplopia, dysphagia, dysarthria, blindness, blurred vision, dark vision, dim vision, deafness, temporary confusion or loss of memory, and unconsciousness. Characteristically, the complaints are bilateral in vertebral-basilar disease and unilateral in middle, anterior, posterior, and internal carotid artery involvement. Headache, lightheadedness, veering to one side or the other, and clumsiness or heaviness of a limb are other symptoms,

often difficult to interpret. Numbness and weakness are the two most frequent complaints.

Each of the episodes is rather similar and only minor variations will occur. Usually each attack begins in the same place, that is, the same part of the body tends to be affected first; the extent of spread to other parts may be the same in each attack or may differ, with the hand, face, and foot becoming numb in some attacks, the hand and face in others, and the hand only in still others, each of the attacks starting in the hand. The region of the body affected at the onset of the attack usually shows the most marked neurologic deficit. All of the parts affected may become involved simultaneously or a spread or march may occur from one limb to another. Convulsive movements are rare but have occurred in a few cases. Occasionally the patient reports a feeling that an extremity is moving or tightening up in a fashion difficult to distinguish from a voluntary movement. The attacks are not always easy to differentiate from minor sensory or motor epileptic seizures.

Attacks may last ten seconds, ten minutes, or even an hour. An approximate average duration is two to ten minutes. There may be hundreds of attacks or only a few. They may occur frequently for days or weeks, or they may be spaced at long intervals over a period of months or even several years. Judging from the frequency with which stroke patients give a history of premonitory symptoms, it would seem that the most common outcome of a series of episodes is the development of a stroke. The final full paralysis may be preceded by hundreds of attacks over a period of weeks, or there may be only a few or even a single one the day before. However, in some cases the episodes, after persisting for days or weeks, cease without culminating in a stroke, and for this reason it is extremely difficult to predict the outcome in each case. This uncertainty also makes the evaluation of therapy difficult.

Not infrequently, as the attacks continue, they no longer are completely reversible and an increasing neurologic deficit gradually appears. At any time a full blown stroke may be precipitated, often during sleep or shortly after arising.

The mechanism of the recurrent ischemic attack is far from a settled matter. Formerly they were designated as attacks of "cerebral vasospasm," and this concept is in agreement with their brevity, repetitiveness, and complete reversibility. However, as yet there is no proof that vasomotor phenomena play any part. As already pointed out, the attacks are closely related to atherosclerosis and thrombosis and usually appear when the local cerebral circulation is about to fail completely with disastrous results. Precipitation of the attacks has been attributed to a transient fall in the systemic blood pressure, although such a fall is usually not detectable at the bedside. It has been shown that anticoagulants abolish the attacks in most cases but it is not clear how this is achieved.

Recurrent focal cerebral ischemic attacks must be differentiated from epileptic seizures, recurrent embolism, various neurologic conditions (tumors, cysts, and so on), labyrinthine dizziness, fainting spells, migraine, and nervous giddiness, as well as many undecipherable complaints of the elderly.

B. TRANSIENT CEREBRAL ISCHEMIA WITH SYSTEMIC HYPOTENSION

Two subtypes have been included here in order to separate hypotension followed by a focal neurologic deficit (numbness, weakness, dysphagia, dizziness, and so on) from hypotension attended by fainting or syncope with presumably no evidence of localization of the cerebral ischemia. Although ordinary syncope is not usually to be confused with a stroke, it is, of course, a circulatory disorder and must be included in this outline of cerebrovascular disorders.

The type with focal neurologic deficit was alluded to in section I C, where it was pointed out that a severe fall in the systemic blood pressure can, by diminishing the cerebral blood flow, lead to focal ischemia distal to an atherosclerotic narrowing which had previously been tolerated or adequately compensated for under normal conditions of blood pressure. If the period of hypotension is only brief, ischemic damage is reversible and neurologic function returns promptly when the blood pressure is restored. The causes of systemic hypotension are "simple fainting," acute blood

loss, acute myocardial infarction, traumatic and surgical shock, Stokes-Adams syndrome, carotid sinus sensitivity, cardiac arrest or anesthetic accident during surgery, and severe postural hypotension (idiopathic, postoperative, induced by sympathetic blocking agents, and reserpine, post-sympathectomy, diabetic, tabetic, and so on). The mechanism by which transient symptoms are produced under these circumstances proably resembles that which leads to recurrent episodes preceding the onset of a stroke; one striking difference, however, is the existence of an *obvious* cause for the attack, namely, severe hypotension. The term "recurrent" is not applicable to this group, as there will be but one episode unless the hypotension recurs. The clinical manifestations will depend on the site of the vascular obstruction and the territory involved. The remarks made concerning syndromes under cerebral thrombosis and recurrent focal cerebral ischemic attacks apply here.

C. MIGRAINE INCLUDING MIGRAINOUS HEMIPLEGIA

The aura of migraine (flickering scotomata, numbness, weakness, dysphasia, and so on) is usually attributed to transient cerebral ischemia resulting from local vasoconstriction. The repeated occurrence of a degree of arterial narrowing just sufficient to produce ischemic manifestations and yet rarely severe enough to lead to permanent damage is a most extraordinary phenomenon concerning which there is very little fundamental information. Occasionally, however, the paralysis, sensory change, or speech disturbance following migraine may take several days to clear and it rarely remains permanently.

III. INTRACRANIAL HEMORRHAGE (including intracerebral, subarachnoid, ventricular, and subdural forms)

The possibility of intracranial hemorrhage comes up for consideration in most stroke cases. It might be claimed that, in deciding the nature of a stroke, the clinician probably unconsciously first differentiates between hemorrhage and infarction (there are only these two possibilities), and when hemorrhage has been ruled out (clinical opinion being bolstered by the absence of blood from the cerebrospinal fluid), he then proceeds to distinguish between thrombosis and embolism.

Intracranial hemorrhage accounts for about 25 per cent of cerebrovascular lesions found at postmortem examination. Although 12 different causes have been listed, the first two, hypertensive intracerebral hemorrhage and ruptured saccular aneurysm, are by far the most important and account for most of the hemorrhages which give rise to the clinical picture of a stroke. Duret hemorrhages, hypertensive encephalopathy, and idiopathic brain purpura are included for the sake of completeness and are not likely to simulate a stroke.

A. HYPERTENSIVE INTRACEREBRAL HEMORRHAGE

This is the ordinary, well recognized cerebral hemorrhage. For practical purposes it is *almost always associated with high blood pressure.* While at times the hypertension is not excessive, reaching levels of only 160 or 170 over 90, in most cases it is much higher. The elevation of blood pressure is maintained early in the course of the intracerebral hemorrhage and, indeed, may even rise to greater levels so that the existence of hypertension is easily established at the time the patient is first examined.

The great majority of intracerebral hemorrhages occur while the patient is *up and active* and onset during sleep is a great rarity. There are *no warning or prodromal symptoms* and the patient is stricken suddenly. *The stroke develops gradually* over a period of minutes, hours, or occasionally days, the average time being (approximately) one to six hours.

The clinical manifestations depend partly on the site of the hemorrhage and partly on the speed of the bleeding. Some 40 per cent of hemorrhages are in the region of the putamen and adjacent internal capsule (capsular), the other regions of predilection being thalamus, pons, cerebellar hemisphere, and various parts of the central white matter. The most characteristic picture in cases of putaminal or thalamic hemorrhage is as follows: The patient suddenly complains of something going awry within the head. In a few minutes speech is slurred or dysphasic and the hand and foot become weak. Gradually the paralysis worsens, speech becomes impossible, and

confusion gives way to stupor. In the worst cases, coma supervenes and the patient dies within a period of a few hours up to 24 or 48 hours. Contrary to former opinion, all cases of cerebral hemorrhage do not become comatose promptly and not infrequently the spinal fluid is grossly bloody at a time when the patient is capable of replying to questions and responding to commands. In 25 to 30 per cent of cases, the hemorrhage ceases and the patient survives.

When the hemorrhage is situated in the pons, consciousness is lost rather promptly and death usually occurs within a few minutes or hours. In cerebellar hemorrhage, vestibular dizziness, vomiting, and ataxia appear first and, if the hemorrhage is to be fatal, coma quickly follows. But in each of these sites, bleeding may be arrested and the patient may recover.

Hemorrhage almost invariably arises within brain tissues, that is, intracerebrally, and rupture of arteries lying in the subarachnoid space is practically unknown, apart from saccular aneurysm. Therefore, it is a mistake to think of hypertensive hemorrhage as arising from the large arteries at the base of the brain. The extravasation, forming a roughly circular mass, grows in volume as the bleeding continues. Adjacent brain tissue is displaced and compressed, midline structures are shifted to the opposite side, and vital central structures are compromised. Finally, rupture or seepage into the ventricular system usually occurs and the spinal fluid becomes bloody. If the hemorrhage is small and placed at a distance from the ventricular surface, the cerebrospinal fluid may remain clear even on repeated examination. This is the exception, however, and one can *expect to find red blood cells or xanthochromia* in the cerebrospinal fluid in the majority of intracerebral hemorrhages.* The cerebrospinal fluid pressure will also be raised. Hypertensive intracerebral hemorrhages rarely rupture through to the subarachnoid surface of the hemisphere. If the patient survives the acute phase of the illness, recovery of function may be surprisingly complete, since the brain tissues are damaged to a considerable extent by displacement and not utterly destroyed as in infarction. It takes many months for extravasated blood to be removed, but finally only an orange-colored slit marks the site of the former hemorrhage.

The nature of the vascular lesion which leads to arterial rupture is not known and indeed the site of rupture has not often been identified. Atherosclerosis is held by many to be a factor but there is no proof for this view, and hemorrhages are encountered in the absence of grossly visible atherosclerosis. One theory attributes the hemorrhage to a confluence of myriads of smaller diapedetic hemorrhages, but this hypothesis must be abandoned. The different rates at which hemorrhages progress is probably related to the size of the vessel which has ruptured. Bleeding seems to be an *all or none* process and resumption or recurrence of hemorrhage is rare. This is quite different from hemorrhage from a saccular aneurysm which is intermittent in the majority of cases.

B. RUPTURED SACCULAR ANEURYSM

This very important disorder presents one of the most pressing therapeutic problems of the day. Saccular aneurysms take the form of small, thin-walled blisters protruding from the arteries of the circle of Willis or the major vessels arising therefrom. These saccules or berries, as they have been called, are situated at bifurcations and branchings and presumably are the result of developmental defects in the media and elastica at these sites. Due to weakness of the wall, the intima protrudes outward and, covered by adventitia, the outpouching gradually enlarges until dissolution of the wall and rupture finally occur. Atherosclerosis, although present in the walls of many such aneurysms, probably plays no part in predisposing to rupture. Saccular aneurysms are rare in childhood but gradually increase in frequency with age to reach a peak incidence in the age period of 35 to 65 years. Therefore, they are really not congenital abnormalities but develop over the years on the basis of a developmental arterial defect.

The most frequent sites are as follows: on the anterior communicating artery, at the origin of the posterior communicating artery from the internal carotid stem, at the first bifurca-

*It is a mistake to think that xanthochromia required several days to develop. Some degree of it can be seen in the supernatant fluid in fresh subarachnoid hemorrhages from any cause, due to the leakage of plasma which contains bilirubin.

tion of the middle cerebral artery, and at the bifurcation of internal carotid artery into middle and anterior cerebral arteries. These sites account for about 85 per cent of saccular aneurysms, the remainder lying on the posterior portion of the circle of Willis, at the junction of posterior communicating artery with the posterior cerebral artery, at the bifurcation of the basilar artery, or at the origins of the cerebellar arteries. To think of aneurysms is to think first of the anterior part of the circle of Willis. In routine autopsies, the incidence of ruptured aneurysms is 1 per cent, of unruptured aneurysms, 1.5 per cent. In size, aneurysms vary from tiny nubbins 2 mm. in diameter up to spherical masses 2 or 3 cm. in diameter. An average diameter is 1 cm. The wall of an unruptured aneurysm may sometimes be so thin and transparent that newsprint can be read through it. Prior to rupture, aneurysms are usually silent and rarely if ever cause headache. Occasionally, when large, they may compress the optic nerve or chiasm, the third nerve, hypothalamus, pituitary, or one of the cranial nerves as it leaves the brainstem.

When rupture occurs, blood under high pressure is discharged into the subarachnoid space (the circle of Willis lies in the subarachnoid space) and the patient is stricken with an excruciating frontooccipital headache. Sometimes the patient remains perfectly lucid, but often consciousness is immediately lost for a period varying from a few seconds to hours, days, or weeks, depending on the severity of the ictus. Highly characteristic of ruptured saccular aneurysm is the tendency for the hemorrhage to cease just as suddenly as it began. Thus, in a typical clinical picture, the patient suddenly develops a severe headache, collapses, becomes unconscious, and regains consciousness a few minutes later, dazed, confused, and complaining of a violent headache. Lumbar puncture will show an extremely bloody spinal fluid under raised pressure. In most cases there are no warning symptoms whatsoever. Aneurysmal rupture usually occurs while the patient is active, rather than resting or asleep. Physical exertion immediately precedes rupture in many cases.

If the hemorrhage is restricted to the subarachnoid space, there will be few or no lateralizing signs and this aspect of the clinical picture is also characteristic of a ruptured aneurysm. Bilateral Babinski signs are found in the early states, especially if there is impairment of consciousness. Mild confusion or impairment of memory may take days or weeks to clear completely. The pathologic picture corresponding to this clinical state shows a thin layer of blood in the subarachnoid space at the base of the brain and along the Sylvian fissures. In cases with more extensive initial bleeding, the hemorrhage may invade adjacent brain tissue and even rupture into the ventricular system. Under these circumstances, lateralizing signs may be more numerous and coma will nearly always be present.

Nuchal rigidity is usually present. Examination of the fundi may reveal smooth-surfaced blobs of blood; these are preretinal or subhyaloid hemorrhages. They usually indicate direct bleeding into the subarachnoid space from an aneurysm or angioma, although they occasionally are seen in cases of primary intracerebral hemorrhage, too. Third nerve palsy (diplopia, ptosis, mydriasis, and oculomotor palsy) is usually indicative of an aneurysm at the junction of the posterior communicating artery and the internal carotid stem, the third nerve lying immediately lateral to this site. Gradually progressive blindness in one or both eyes or sudden blindness in one eye point to an aneurysm of the internal carotid or anterior cerebral artery, as a rule. Convulsive seizures are not uncommon at the onset or in the first week following hemorrhage and are due to local cortical damage. High blood pressure is more often present than not, but many patients show normal pressures. There is an increased incidence of congenital cystic disease of the kidney in association with saccular aneurysm. Coarctation of the aorta may also complicate the picture, especially in the young.

In most cases, the patient survives the first attack of hemorrhage, but recurrence of the bleeding within days, weeks, months, or years occurs in the majority of survivors. There are no rules for prognosticating in which patients rebleeding will occur. Recurrence is more common in the first few weeks than later, but again there is no way of foretelling with certainty who is in immediate danger. Death may

ensue as the result of any of the succeeding hemorrhages, the average number of bleedings in fatal cases being approximately three. By the time the patient comes to autopsy, in 60 to 70 per cent of cases blood has burrowed into the brain (meningocerebral hemorrhage) or into the ventricle as well (meningocerebroventricular hemorrhage). In a few cases the blood passes through the arachnoid into the subdural space, producing a sizable subdural hematoma which may need to be evacuated.

On a conservative regimen the mortality from ruptured aneurysm is higher than 50 per cent, and the need for other therapeutic methods is obvious. Ligation of the carotid artery in the neck and excision of the aneurysm by direct intracranial approach are the two surgical methods used at present and, although the results are encouraging, their exact advantage over conservative care has not yet been established.

C. ANGIOMA

An angioma or hemangioma consists of a tangle of vessels which forms an abnormal communication between the arterial and venous systems. It is a developmental abnormality and not a neoplastic tumor. Angiomas vary in size from small insignifiant blemishes a few millimeters in diameter lying in the cortex to huge masses of tortuous channels which form an arteriovenous shunt of sufficient magnitude to raise the cardiac output. The constituent vessels, which may be of capillary proportions as in the smallest angiomas or reach a diameter of several millimeters in the larger ones, are always abnormal and do not have the usual structure of either an artery or vein. Hence to designate angiomas as capillary, venous, or arterial, is not fully warranted. Angiomas may occupy any site in the brain but are more common in the cerebral and cerebellar hemispheres. When large, they extend from the cortex to the ventricular surface.

The clinical picture takes the form of epileptic seizures, subarachnoid hemorrhage, or both. Commonly the patient is under the age of 25 when symptoms appear, for angioma is a disorder of the young, but on the other hand the first complaints may be delayed as late as the 50's. Seizures are usually focal in type and typically are associated with a temporary postictal paralysis or other neurologic deficit. The possibility of an angioma must be kept in mind in cases of epilepsy dating from early life. When subarachnoid hemorrhage occurs, the picture resembles closely that of ruptured saccular aneurysm, with severe headache, confusion, and bloody spinal fluid under increased pressure. Preretinal hemorrhages may be seen. While high blood pressure is often present, it is axiomatic that the occurrence of intracranial bleeding in association with *normal* blood pressure points to either angioma or saccular aneurysm as the cause. Hemiplegia or other lateralizing signs are frequent, since the angiomatous mass may lie deep and the extravasation take place largely within brain tissue. The first hemorrhage may be fatal, but most often bleeding stops and the patient survives. Recurrence of hemorrhage is the rule. The cause of bleeding is probably "simple rupture" of a vessel, but the underlying vascular change has not been studied.

The patient may complain of a pulsatile noise within the head, and an intracranial bruit may be heard on auscultation, especially if hemorrhage has not yet occurred. This is strong evidence in favor of the diagnosis of angioma. Angiomas apparently may give rise to recurrent headaches and migrainous auras. Roentgenograms of the skull will occasionally show crescentic linear calcifications in the vessel walls of the larger angiomas. Carotid or vertebral arteriography is necessary to establish the diagnosis with certainty.

D. TRAUMA

Although intracranial bleeding due to head trauma does not rightfully fall within the scope of the stroke problem, it must be included here because of the great frequency with which the question of traumatic intracerebral hemorrhage, major or minor, arises in stroke cases in which the history is inadequate or the patient falls and injures himself at the time of the onset of the stroke.

Acute extradural and *subdural hemorrhage* must always be considered in the patient who has suffered an abrupt ictus under known circumstances, whether the spinal fluid is bloody or not. *Chronic subdural hemorrhage* may occur without known trauma and the indefinite picture of drowsiness, mental confusion, and

mild hemiparesis, especially in the elderly, may be erroneously attributed to a stroke. These three conditions must be kept constantly in mind, since failure to make the correct diagnosis deprives the patient of the benefit which surgical intervention offers. There should be no hesitation in placing diagnostic burr holes, a minor procedure, in all cases in which subdural bleeding cannot be excluded on clinical grounds. Cerebral contusion and laceration cause subarachnoid hemorrhage and, if the patient has fallen and struck his head at the time of the onset of the stroke, it may be difficult or impossible to decide if the red blood cells in the cerebrospinal fluid are due to a cerebrovascular stroke or to cerebral contusion. Trauma may also be the cause of acute and delayed intracerebral hemorrhage, acute intracerebellar hemorrhage, brain edema, and widespread focal infarction of undetermined origin.

E. TO L. THE OTHER CAUSES OF INTRACRANIAL HEMORRHAGE

The hemorrhagic hematologic disorders which most commonly give rise to intracranial bleeding are leukemia, aplastic anemia, and thrombopenic purpura. Indeed, in these diseases most of the neuropathologic changes are related to the hemorrhage. Usually this complication signals a fatal issue. Any part of the brain may be involved and not infrequently the lesions are multiple. As a rule, there is evidence of previous abnormal bleeding elsewhere in the body (skin, mucous membrane, kidney, or bowel) when cerebral hemorrhage occurs. The mechanism by which the blood escapes from the vessel is not understood. Occasionally *chronic liver disease* may be associated with an intracerebral hemorrhage, which is usually attributed with some uncertainty to a disturbance of the blood clotting mechanism. Intracranial bleeding is a rare complication of *anticoagulant therapy*.

Hemorrhagic infarction, whether due to arterial or venous occlusion, is characterized by multiple petechial hemorrhages scattered throughout the involved tissue. When arterial occlusion is responsible, the hemorrhages lie chiefly in gray matter, whereas in venous occlusion the extravasation commonly involves both gray and white matter. As previously described, hemorrhagic infarction in which the hemorrhages are for the most part petechial in size does not often present clinically as a hemorrhage and the cerebrospinal fluid is not bloody. However, on rare occasions bleeding within the infarct reaches major proportions, a mass of escaped blood conglobates as in intracerebral hemorrhage, and the spinal fluid becomes bloody.

Brainstem hemorrhage secondary to herniation of the temporal lobe into the tentorial notch usually presents in the form of a complication of acute or subacute expanding intracranial lesions and never as a stroke. It is mentioned here to insure that its real significance is appreciated, especially since it probably is the type of intracranial hemorrhage most frequently encountered at autopsy. Limited to the midbrain and pons, the hemorrhage is usually a confluence of smaller extravasations, probably venous in origin. It is a serious complication of transtentorial herniation and usually spells irreversible coma and death. The hemorrhages are given the name of Duret, who was one of the first workers to observe and describe them.

The category, *hemorrhage of undetermined cause*, is reserved for those not too rare cases in which intracranial hemorrhage occurs in association with normal blood pressure and in which neither an aneurysm nor an angioma can be found. In searching for the cause of obscure intracranial bleeding, neuropathologic examination must be carried out most carefully. In the case of saccular aneurysm, an attempt to identify the sac should be made in the fresh state before formalin has hardened the blood around the basal vessels. It is commonly suspected that a small angioma is usually the basis for intracerebral hemorrhage in normotensive individuals, and in most cases a diligent examination, including microscopic study, will reveal a malformation. *Primary intraventricular hemorrhage* refers to hemorrhages which appear to have arisen within the ventricular system without involving the brain parenchyma proper. An angiomatous malformation of the choroid plexus or ependymal lining may prove to be present, but more often no explanation for the hemorrhage is found. Primary intraventricular hemorrhage is rare.

Hemorrhage into primary and secondary brain tumors. This uncommon complication of tumor is all too likely to present a difficult diagnostic problem. If the hemorrhage is a large one, the clinical picture is that of apoplexy or a stroke, and the clue that the bleeding is secondary and not primary is provided either by the known presence of disseminated carcinomatous lesions or by a history that neurologic symptoms compatible with intracranial tumor growth had preceded the onset of the hemorrhage. The acquisition of this latter information may require careful clinical observation. Hemorrhage into astrocytomas is rare. It is more frequent in pituitary adenoma (pituitary apoplexy), glioblastoma multiforme, or pinealoma. Of the secondary cerebral tumors giving rise to hemorrhage, choriocarcinoma, melanocarcinoma, and hypernephroma are probably the most common.

Septic embolism from the vegetations of acute or subacute bacterial endocarditis has already been considered under infarction, where it was pointed out that a limited amount of hemorrhage could occur into regions of septic infarction. In addition, extensive fatal bleeding may spring from a mycotic aneurysm which has resulted from local inflammation and destruction of the wall of an artery at the site of arrested septic material. As a result of a *focal arteritis* the wall weakens, bulges, and ruptures. Not uncommonly no aneurysmal dilatation can be found at autopsy, merely the ragged edges of the arterial gap. Any part of the circulatory tree may be affected, but usually a mycotic aneurysm occurs at a branching or forking of a small vessel (less than 0.5 mm.) lying in the subarachnoid space. Although the subject of mycotic aneurysm has never been studied thoroughly, it would appear that its rupture is an all-or-none phenomenon which is often fatal. Since the introduction of the newer antimicrobic agents, the condition is seldom encountered clinically or pathologically.

Hypertensive encephalopathy is described in section V. Here it may be stated that the term is reserved for the acute clinical disorder characterized by severe hypertension (usually the diastolic pressure is at least 120 mm. Hg), headache, vomiting, stupor, seizures, and coma. At autopsy the swollen brain may show a typical large hypertensive intracerebral hemorrhage, several smaller ones, 0.5 to 1 cm. in diameter, or multiple petechial hemorrhages.

Idiopathic brain purpura does not really belong in this group, since it is perhaps more closely related to toxic diseases of the brain. Anatomically it consists of multiple petechial hemorrhages scattered throughout the white matter of the brain. At one time the most frequent example of this condition was "arsenical hemorrhagic encephalitis" which complicated the treatment of syphilis. The clinical picture is that of a diffuse cerebral disease, with bilateral neurologic signs, stupor, coma, and death. There is never any blood in the cerebrospinal fluid and the condition will never be confused with a typical stroke.

Inflammatory diseases of arteries and veins have been included here in order to accommodate the cases of hemorrhage associated with lupus erythematosus and polyarteritis nodosa (considered in section VI). In lupus erythematosus, medium-sized, atypically situated, intracerebral hemorrhages may be found in the absence of hypertension which so often results from renal involvement. Usually the diagnosis of the systemic disease will have been made long before cerebral hemorrhage occurs. Polyarteritis does not often extend to the intracerebral vessels and, therefore, hemorrhage from this cause is rare. As already mentioned, a mycotic aneurysm is really the product of a local arteritis.

IV. VASCULAR MALFORMATIONS AND DEVELOPMENTAL ABNORMALITIES

Of the conditions listed under this heading, only ruptured saccular aneurysm and angioma relate directly to the problem of strokes, and both of these were discussed in the section on intracranial hemorrhage. However, reference is often made in clinical neurology to the other abnormalities and, therefore, a brief note concerning them is included.

A. ANEURYSM

Due to our incomplete knowledge of the pathogenesis of the different types of intracranial aneurysm, there is at present no satisfactory classification of them. The origin of saccular aneurysms, as already described, probably rests on the existence of developmental

defects in the media and elastica of the large cerebral arteries, especially at bifurcations and branches. Their main effects on the nervous system result from rupture, that is, subarachnoid and meningocerebral hemorrhage (described in section III) and ischemia.

Fusiform, diffuse, and globular aneurysms are often assumed to be developmental in nature, but this has not yet been proved. These aneurysms consist of enlargement of the entire circumference of the artery and their names reflect the predominant shapes or morphologic aspects. *Fusiform aneurysms* are relatively circumscribed, spindle-shaped dilatations involving either the internal carotid arteries within or near the cavernous sinus or the basilar artery. In the *diffuse* variety the aneurysm takes the form of an extensive tubular enlargement extending over several centimeters, and again involves the internal carotid, middle cerebral, or the vertebral-basilar systems. In the latter the appearance is typically S-shaped. Fusiform and diffuse aneurysms are commonly attributed to arteriosclerosis, but both are encountered occasionally in the younger age groups unassociated with arteriosclerosis and, furthermore, they may be bilateral. On the other hand, in most cases of atherosclerosis, no such enlargement occurs. For these reasons there is justification for the suggestion that these aneurysms are due at least in part to developmental factors. *Globular aneurysms* comprise a distinct group in which strikingly spherical dilatations occur in either the vertebral or internal carotid arteries, the parent vessel entering at one pole and leaving from the opposite. This type occurs in the younger age group and hence is probably of developmental origin.

Fusiform, diffuse, and globular aneurysms do not often rupture and bleed, but they evoke symptoms either by exerting pressure on neighboring structures or by undergoing thrombosis.

B. ANGIOMA

The clinical picture associated with hemangioma has been described (section III C), but for the sake of completeness two further syndromes are mentioned here – familial telangiectasis and retinal-pontine angiomatosis. It should be emphasized that angiomas may be widespread, involving more than one organ.

C. TRIGEMINAL ENCEPHALOANGIOMATOSIS (Sturge-Weber-Dimitri Disease)

In this developmental disorder a localized degeneration of the cerebral cortex is found in association with a port-wine stain (capillary angioma) of the face in the first division of the trigeminal nerve. The cortex subjacent to the angioma often calcifies and casts a double contour shadow on the roentgenogram. The cerebral lesions, which scarcely ever bleed, may be associated with mental retardation, epilepsy, and focal neurologic deficit in the form of hemiplegia.

D. VARIATIONS IN THE CEREBRAL ARTERIES

The circle of Willis is subject to countless variations in the relative size of its constituent vessels. However, only when vessels are either absent or thread-size are these modifications of potential importance in determining the availability of collateral blood flow in case of vascular occlusion. Anomalies of the circle of Willis are at times attended by unusually severe atherosclerosis. In interpreting the extent and topography of cerebral infarction, the pattern of the basal arteries may be of crucial importance. The following vessels may be extremely small: the anterior cerebral stem, so that its mate of the opposite side supplies both anterior cerebral territories; the anterior communicating artery, with the result that blood cannot be shifted from one carotid system to the other; one or both posterior communicating arteries, so that potential flow between the basilar and carotid systems is limited; one or both posterior cerebral stems, the posterior cerebral territory being supplied from the carotid system, with the result that the basilar system is isolated from the carotid system; or one vertebral artery, so that occlusion of the opposite vertebral is almost equivalent to blockage of the basilar artery.

Rarely, one or both internal carotid arteries are missing. Among the abnormal communications encountered in the cerebral arteries, the carotid-basilar anastomosis via the cavernous sinus might be mentioned.

V. INFLAMMATORY DISEASE OF ARTERIES

The arteritides produce clinical manifestations chiefly by giving rise to infarction or

hemorrhage, which have been discussed. Here the various types are assembled for the convenience of the reader, to enable him to survey this somewhat heterogeneous field at a glance.

A. INFECTIONS AND INFESTATIONS

Meningovascular syphilis would have outnumbered all the other types combined a few years ago, especially in the younger age groups but, owing to the remarkable therapeutic efficacy of antibiotics and the decreasing incidence of the disease, this holds true no longer. Neurosyphilis is basically a chronic meningitis and the subarachnoid vessels of the brain and spinal cord lying within this inflamed meshwork become involved secondarily. If the arteritic process extends to the intima, connective tissue proliferation and/or thrombosis results, with cerebral infarction as a consequence. The small penetrating vessels are affected chiefly, producing a succession of infarcts in the brain, usually with small strokes rather than catastrophic ones. It may be said almost categorically that intracranial hemorrhage and aneurysm are never the product of the treponema pallidum. Syphilis must still be excluded in all stroke cases due to infarction. The cerebrospinal fluid will invariably show evidence of active inflammation in the form of increased cells and an increased protein level. Advancing neurosyphilis should never be diagnosed in the presence of an inactive cerebrospinal fluid.

Just as syphilitic meningitis gives rise to cerebral arterities and thrombosis, *pyogenic* meningitis (influenzal, staphylococcal) and *tuberculous meningitis* do likewise. Of course, the primary diagnosis will in all probability have been made previously and the picture will not closely resemble a typical stroke. Occasionally, however, tuberculous meningitis first announces itself by the precipitous onset of a hemiplegia or other major neurologic deficit. The focal arteritis and resultant mycotic aneurysm produced by *septic embolism* have been mentioned previously.

Rare types of arteritis include typhus, schistosomiasis mansoni, Mucor mycosis, malaria, trichinosis, and the like. In typhus and other of the rickettsial diseases, capillary and arteriolar changes and perivascular inflammatory cells are found in the brain and presumably underlie the convulsions, coma, and confusional psychoses which may occur. A characteristic vascular lesion in the brain is induced by *Schistosoma mansoni*, leading to occlusion of small arteries and focal brain lesions. The internal carotid artery may be occluded by Mucor mycosis in cases of diabetes mellitus.

In trichinosis, aside from the muscular weakness associated with involvement of the muscle fibers by the parasites (ophthalmoplegia and lingual weakness), there may be an abrupt onset of convulsions, aphasia, hemiplegia, and coma. There is still uncertainty regarding the pathogenesis of cerebral symptoms, but in at least one case known to the authors the cerebral lesions were produced by bland emboli arising in the heart and related to a severe myocarditis. Malaria of the malignant or falciparum variety is often attended by a clinical state known as "cerebral malaria." The onset is acute, with hyperpyrexia, convulsions, deepening coma, and, if death is delayed or prevented by therapy, further clinical evidence of focal brain involvement such as paralysis, aphasia, and so on. The cerebral capillaries and precapillaries are occluded by agglutinated masses of parasitized red blood cells and surrounded by petechial hemorrhages and foci of tissue necrosis (malarial granulomas). The inclusion of trichinosis and malaria in the arteritides may be open to question, since the arterial lesions rarely take a frankly inflammatory form.

B. UNDETERMINED ORIGIN

Arteritides of undetermined cause do not commonly involve the cerebral arteries. Nevertheless, it is necessary to be aware of their existence, especially when an exact interpretation of the nature of a stroke is the necessary prelude to the use of potentially dangerous therapy such as anticoagulants.

Systemic lupus erythematosus is the most frequently occurring representative of this class of disease and it may be accompanied by neurologic manifestations related to both the peripheral and central nervous systems. Delirium, confusional states, convulsions, and hemiplegia, aphasia, or other focal signs mark the onset of cerebral involvement. In cases with severe renal disease, intracerebral hemor-

rhage or hypertensive encephalopathy may terminate the illness. Neuropathologic alterations include changes in the arterioles and small arteries, with microinfarcts. Also, there may be embolic occlusion of large and small brain arteries secondary to verrucous endocarditis (Libman-Sacks).

Rheumatic arteritis is still a debatable topic. There is, as indicated above, a high incidence of brain embolism in acute rheumatic fever or in the chronic endocarditic stage of the disease. But, in addition, there have been many claims made for a specific inflammatory disease of small arteries. This possibility cannot be dismissed, although neuropathologic studies are few and unconvincing. Inasmuch as rheumatic fever and lupus erythematosus are closely related, all that has been said of the vascular lesions of one applies to the other.

Polyarteritis nodosa seldom involves the cerebral arteries and, when it does, it tends more to implicate small rather than medium-sized arteries, giving rise to a subacute granulomatous inflammatory exudate with giant cells rather than the more typical necrotizing lesion. This noninfective granulomatous form also affects pulmonary vessels. The neurologic picture is not usually that of a stroke but rather an acute or subacute progressive cerebral syndrome, simulating brain tumor or encephalitis in which headache, convulsions, confusional psychoses, ataxia, and hemiparesis are prominent. A moderate increase in white blood cells and protein in the cerebrospinal fluid may provide further evidence that the cause of the illness is not one of the more common types of vascular disease. With severe renal involvement or as a complication of steroid therapy, severe hypertension may supervene and lead to either a hypertensive brain hemorrhage or hypertensive encephalopathy.

Cranial arteritis (temporal arteritis) is an uncommon affliction in which branches of the external carotid artery, especially the temporal arteries, are the site of a subacute inflammation, with an exudate of lymphocytes, polymorphonuclear leukocytes, and giant cells which leads to thrombosis. This aspect of the disease, although distressingly painful, is not serious otherwise. However, in over 35 per cent of cases, blindness, bilateral or unilateral, complete or incomplete, transient or permanent, complicates the benign course of the illness. Arteritic involvement of the ophthalmic and other small nutrient vessels of the optic nerve is probably responsible, but no pathologic studies have been made. Cranial arteritis, chiefly affecting the elderly, is related to stroke only in the differential diagnosis of isolated peripheral blindness and chronic vascular headache. It is probably one of the most frequently overlooked of the vascular syndromes.

Finally, there is *idiopathic granulomatous arteritis* of the aorta and its major branches, including the common and internal carotid arteries. Described long ago in Japan (Takayasu's disease) and later in Norway, examples have occurred from time to time in all countries. In Japan the disease appears to be particularly frequent in adolescent and young adult women and gives rise to a "pulseless" syndrome due to an occlusion of carotid and limb arteries. The vascular pathology is not well defined, but chronic inflammation with destruction of all coats of the vessel, infiltrates of lymphocytes, plasma cells, and mononuclear leukocytes, presence of giant cells, and occlusion by thrombi comprise the lesion. Bilateral occlusion of the carotid arteries results in a neurologic picture similar to that of the more common pulseless disease of older people, which is caused by atherosclerosis. The nature of the disease is unknown. It has in the past been confused with cranial arteritis and so-called Winiwarter-Buerger's endarteritis obliterans. Along with embolism and angioma, it should be considered in cases of unexplained stroke in young adults.

Thromboangiitis obliterans of Winiwarter and Buerger is not included in the classification. Despite the large number of reported cases with involvement of the carotid and other brain arteries, it has proved in every instance coming to our notice to be atherosclerosis or a "giant cell arteritis" of unknown cause.

VI. VASCULAR DISEASES WITHOUT CHANGES IN THE BRAIN

This category has been included in order that the pathologist may find the arterial diseases which he encounters upon gross and microscopic examination of the brain. Some of these types of vascular disease need no further description here, for example, cerebral athero-

sclerosis and hypertensive arterio- and arteriolosclerosis.

Hyaline changes in the cerebral arteries are particularly common in the presence of long-standing hypertension. The media loses its characteristic smooth muscle structure and stains a uniform pale pink in the hematoxylin and eosin stain. Hypertensive intracerebral hemorrhage is considered by some to arise on the basis of this "hyalinosis."

The carotid arteries within the cavernous sinus are frequently calcified and are often seen on routine roentgenograms of the skull. Although commonly attributed to secondary change within atherosclerotic plaques, the degree of calcification does not seem to parallel the severity of atherosclerosis. *Ferruginization (calcinosis)* is characterized by the presence of a purple-staining material which is often (50 per cent of elderly adult brains) found deposited in the vessel wall and in the surrounding brain tissue, especially in relation to the arteries of the basal ganglia, hippocampus, and dentate nuclei of the cerebellum. For the most part, it is of no known significance clinically. *Capillary sclerosis* refers to the presence of increased numbers of silver-staining connective tissue fibrils around brain capillaries. Its significance is not known, although several cerebral diseases of obscure etiology, such as senile dementia, have been attributed to it without sufficient evidence.

VII. HYPERTENSIVE ENCEPHALOPATHY

This term is used here to refer to an acute syndrome in which severe hypertension is associated with headache, nausea, vomiting, confusion, convulsions, stupor, and coma. Chronic hypertensive encephalopathy is not recognized as an entity and, therefore, the designation acute is not needed for the foregoing syndrome. Usually by the time this neurologic syndrome appears, the hypertension has reached a malignant stage, with papilledema and threatening failure of kidneys and heart. The nonprotein nitrogen level of the blood may be raised. The hypertension may be "essential" or due to chronic renal disease, pheochromocytoma, Cushing's syndrome, or ACTH toxicity. When hypertensive encephalopathy is associated with acute glomerulonephritis, symptoms may develop when the hypertension is very moderate in degree. Eclampsia has been listed by itself to underline the special circumstances under which it occurs, rather than to indicate a separate pathogenesis.

Formerly hypertensive encephalopathy heralded the end-stage of hypertensive disease, but now the reduction of blood pressure through the use of hypotensive drugs may sometimes reverse the picture within a few days or even less. Neuropathologic examination in fatal cases may reveal a rather normal-looking brain, but usually there is one or several of the following: cerebral edema, large and small hemorrhages, petechial hemorrhages, clusters of glial cells, microinfarcts, and vascular alteration and necrosis. In view of the general reversal of symptoms following lowering of the blood pressure, these pathologic changes must occur only late in the illness, since they could not be dissipated in so short a time as a day or two.

VIII. DURAL SINUS AND CEREBRAL VENOUS THROMBOSIS

Although intracranial phlebothrombosis and thrombophlebitis will not often mimic the picture of a stroke, they are important forms of vascular disease. As a result of occlusion of the veins or sinuses, blood is dammed back into the small vessels and capillaries. If venous drainage is sufficiently obstructed, local ischemia of brain tissue ensues, to be followed by cerebral edema and hemorrhagic infarction. When the effect is less severe, there may be only partial ischemia of the cerebral cortex, which is presumably the basis for the frequent occurrence of focal epileptic seizures. In still milder form, occlusion may be altogether asymptomatic or may manifest itself as an increase in the intracranial venous pressure and a rise in the cerebrospinal fluid pressure.

Vein and sinus thromboses are most often secondary to pyogenic infections of the mastoid, paranasal sinuses, or face. The acute inflammatory process reaches the larger veins directly, via local osteomyelitis or by evoking thrombophlebitis of small diploic vessels which then extends through emissary veins to the larger radicles. Although much less common than before the introduction of antibiotics, this condition remains a serious complication of infections of paracranial structures. Pyogenic

meningitis and acute subdural empyema may also involve the veins in the neighborhood of the infection.

In addition to its occurrence secondary to infection, thrombosis of cerebral veins is also found in association with cachexia, particularly in children, and not too infrequently within the two or three weeks following childbirth or a surgical operation. The postpartum variety has excited much interest, being due presumably to a natural hypercoagulability of the blood that occurs a few days after delivery (hyperfibrinogenemia or increased blood platelets). Hematologic disorders, such as polycythemia and sickle-cell disease, are commonly held to be causes of cerebral venous thrombosis. A few cases are seen in association with cardiac failure or congenital heart disease.

The clinical picture varies, of course, with the nature of the primary disease, the extent of the pathologic process, the veins involved, and the effects of venous damming on brain tissue. The manifestations range from widespread hemorrhagic infarction associated with seizures, hemiplegia first on one side of the body and then the other, coma, and bloody cerebrospinal fluid, to a series of one-sided seizures followed by transient motor or sensory paralysis or aphasia with only a few white blood cells in the cerebrospinal fluid. The presence of a monoplegia involving leg and arm, but sparing the face, may suggest that the lesion lies in the upper part of the hemisphere adjacent to the sagittal sinus, a common site for infarction if sagittal sinus occlusion has occurred. Bilateral neurologic signs, especially bilateral focal seizures arising from the superomedial part of the hemisphere, also suggest sagittal sinus disease. As already mentioned, occlusion of the sagittal or transverse sinuses may result in an increase in the cerebral venous pressure and secondarily in a raised intracranial cerebrospinal fluid pressure. Clinically this may give rise to severe headache, papilledema, and visual obscurations without any other neurologic abnormality, a baffling syndrome unless its true nature is appreciated.

The changes in the cerebrospinal fluid will reflect the pathologic process. There may be only a few extra white cells and a rise in the pressure, but where cerebral damage is extensive with hemorrhagic infarction, the fluid may be bloody and under high pressure. If it complicates a purulent meningitis, of course, the white cells are greatly increased due to the presence of inflammation.

IX. STROKES OF UNDETERMINED ORIGIN

This is a clinical rather than a pathologic category, since it is usually possible to distinguish hemorrhage from infarction at autopsy. This is not true of strokes seen at the bedside, and in many cases where the history is faulty and the spinal fluid free from evidence of bleeding, there is no choice but to classify the stroke as of undetermined origin.

CLINICAL DIAGNOSIS OF CEREBROVASCULAR DISEASE

Until comparatively recent times no premium could be put upon the accurate diagnosis of cerebrovascular disease. It was sufficient for the physician to appreciate that the patient was suffering from a stroke, and its type was of little consequence. If the stroke was mild, the patient would recover; if severe, he would succumb. As every thoughtful physician knew, accurate diagnosis could only serve the interest of the patient if it led to correct and effective therapy, and, for the group of cases under consideration, there had been no accepted mode of therapy since the abandonment of the purgings, bleedings, and empirical medicinals of the medieval period.

Now the situation is changing. Powerful drugs are at hand which alter the coagulability of the blood, dilate blood vessels, suppress endocardial and hemic infections, reduce the cerebral blood pressure from dangerously high levels, and elevate it after circulatory collapse. Ingenious neurosurgical technics have been devised for the control of arterial hemorrhage and removal of clot or the replacement of a diseased segment of artery by an arterial graft. While it is true that we have not yet learned the proper application or assessed the effects of all these methods, nonetheless one can hardly consider their adoption until diseases as different as ruptured aneurysm, hypertensive hemorrhage, embolism, and thrombosis can be recognized clinically. Diagnosis now becomes imperative in cerebrovascular disease, not alone as a means of directing therapy, but also for the segregation of cases for scientific

study and foretelling the outcome of a given case, with or without treatment.

When confronted with a fresh case of cerebrovascular disease, each of us, no doubt, has his individual method of approach, but probably all would agree that the problem of diagnosis is usually resolved in a succession of orderly steps. These can be propounded in the form of several questions. 1) Does the patient have a vascular disease of the brain or some other type of neurologic abnormality? 2) If it is a cerebrovascular stroke, is the main process one of hemorrhage or infarction? 3) If infarction, is the cause atherosclerosis of brain arteries, embolism, arteritis, or venous thrombosis? 4) If hemorrhage, is it a ruptured aneurysm or other vascular malformation or a hypertensive hemorrhage?

Regarding the initial problem of whether the disease is vascular in nature, we have already stated that diagnosis rests solely on the recognition of the cerebrovascular stroke or apoplectic state and without evidence of this, the diagnosis must always be in doubt. Two criteria have already been stated as having practical utility in the identification of the cerebrovascular stroke:

1. Evidence of focal brain disease.
2. The temporal profile of the clinical syndrome.

The finding of relatively crude neurologic signs, such as hemiplegia, brachial or crural monoplegia, aphasia, hemihypesthesia or sensory disturbances in the face, arm or leg, homonymous hemianopia or monocular blindness, agnosia, unilateral cerebellar ataxia, nystagmus, ocular or gaze paralysis, dysphagia, or dysarthria, provides unequivocal evidence of the *focal character of the brain disease*. More difficult to evaluate are the evanescent symptoms which may have disappeared before the physician is called. They must be distinguished from the other paroxysmal and transitory neurologic states, such as convulsion, syncope, rotational vertigo, concussion, migraine attack, episodic coma of toxic or metabolic cause, and anxiety state.

The *temporal profile* can usually be ascertained by a clear history of the mode of onset, evolution, and course of each symptom taken in relationship to the medical status at the time of examination. If these data are lacking, the course may be determined by extending the period of observation over a period of days or weeks, adhering to the old clinical adage that the physician's best diagnostic tools are the second and third examinations. Without a satisfactory knowledge of the clinical course, it may be impossible to distinguish cerebrovascular disease from the other focal diseases of the brain, such as tumor, subdural hematoma, abscess, encephalitis, and acute demyelinative disease of the brain.

In the circumstance that a given medical case has an obvious cerebrovascular origin, the second logical step requires discrimination between hemorrhage and infarction. Usually one is concerned with the differentiation of brain infarction from hypertensive brain hemorrhage and less often from a massive bleeding from an aneurysm or angioma. In many instances the differentiation can be made on the basis of clinical manifestations summarized below, but examination of the spinal fluid for the presence or absence of blood remains the most reliable method, keeping in mind that a minority of intracranial hemorrhages do not produce bloody spinal fluid. Blood in the cerebrospinal fluid is found in *hypertensive hemorrhage, ruptured saccular aneurysm, ruptured vascular malformation, septic embolism with mycotic aneurysm, venous thrombosis with hemorrhagic infarction,* and occasionally *aseptic arterial embolism with hemorrhagic infarction.* Hemorrhagic diseases and cranial trauma should also be included.

Intracerebral hemorrhage is characterized by:

1. Grossly bloody cerebrospinal fluid.
2. Hypertension.
3. Rapid evolution of hemiplegia and other phenomena over minutes or hours.
4. Onset generally during activity.
5. Rapid progression to coma.
6. Headache* (if patient is sufficiently conscious to report his feelings).

*Headache occurs almost invariably in hemorrhage, but it may also occur in atherosclerotic thrombosis. Absence of headache is a strong point against the diagnosis of intracranial hemorrhage.

A common source of error in lumbar puncture is to mistake a "bloody tap" for subarachnoid hemorrhage, or vice versa. A bloody tap may result in tinging of the cerebrospinal fluid for several days, at first with blood and later with bilirubin. In subarachnoid hemorrhage the cerebrospinal fluid is usually under increased pressure; there is an even admixture of blood in all samples, a failure of the cerebrospinal fluid to clot (already defibrinated in subarachnoid space), and a definite xanthochromia of the supernatant fluid. In a bloody tap the cerebrospinal fluid pressure is normal or low, the fluid that first flows from the needle is more bloody than later samples, the fluid often clots, and xanthochromia is present only in proportion to the amount of serum bilirubin in the fluid. Bloody taps can often be avoided if the lumbar puncture is performed with great care.

The clinical criteria of *"primary" subarachnoid hemorrhage* are:

1. Sudden onset of severe headache.
2. Stiff neck on forward bending, Kernig and Brudzinski signs.
3. Grossly bloody cerebrospinal fluid.
4. Absence of focal neurologic signs.
5. A relatively transitory disturbance of consciousness.
6. Subhyaloid (preretinal) hemorrhages.

Intracranial hemorrhage from a vascular malformation becomes a tenable diagnosis under the following circumstances:

1. Repeated subarachnoid hemorrhages (sometimes more than five).
2. Antecedent epilepsy or focal cerebral symptoms.
3. Presence of a cranial bruit.
4. Stroke in a young patient with bloody cerebrospinal fluid in the absence of hypertension.
5. Subhyaloid (preretinal) hemorrhages and retinal angiomas.
6. Characteristic calcification in skull roentgenogram.

The existence of acute leukemia, aplastic anemia, thrombopenic purpura, and cirrhosis of the liver always favors the diagnosis of intracranial hemorrhage due to hemorrhagic disease, especially if other hemorrhagic manifestations are evident.

In cerebral infarction the perturbation of brain function, as evidenced by coma or stupor, is usually less pronounced than in intracranial hemorrhage. A cerebrovascular stroke which leaves the mind untouched or altered only slightly is usually due to an infarct.

The diagnosis of *infarction due to atherosclerotic arterial thrombosis* rests on the following:

1. Prodromal episodes, "warnings" (recurrent cerebral ischemic attacks), often with recovery or improvement between attacks.
2. More gradual evolution with progression of individual symptoms over a period of minutes to hours or longer, or saltatory progression.
3. Relative preservation of consciousness.
4. Clear cerebrospinal fluid.
5. Rapid improvement at times.
6. Certain constellations of symptoms and signs; for example, lateral medullary syndrome, rarely seen with embolism.
7. Evidence of atherosclerosis elsewhere, especially coronary and peripheral vessels and aorta.
8. The presence of disorders commonly associated with atherosclerosis (hypertension, diabetes mellitus, xanthomatosis).

The diagnosis of arteritis as a source of infarction is justified only with evidence of an arteritis elsewhere, in young individuals who manifest neither hypertension nor signs of cardiovascular disease, and in individuals with a meningeal infection which could affect the meningeal vessels (syphilis, tuberculosis). Venous thrombosis with infarction should be especially considered when focal neurologic signs develop after an operation or in women after parturition, in the course of a meningeal infection, in ear or sinus suppuration, in any disease which results in cachexia, and in sickle-cell disease or polycythemia.

The diagnosis of *embolic arterial occlusion* is indicated by the following phenomena:

1. The cerebrovascular symptoms have developed suddenly (within seconds or a few minutes).

2. Absence of prodromal manifestations in most cases.
3. Relative preservation of consciousness.
4. Clear cerebrospinal fluid.
5. Rapid improvement at times.
6. Focal neurologic signs or special arterial syndromes.
7. A source of emboli exists usually in the heart (either cardiac arrhythmia or infarction).
8. Evidence of recent embolism in
   a. other organs (spleen, kidney, extremities, intestines, or lungs)
   b. several regions of the brain in different cerebrovascular territories.

LABORATORY METHODS OF DIAGNOSIS

There are a number of special laboratory tests which are valuable in the diagnosis of cerebrovascular disease, but none of them can approach in general usefulness a careful history and physical examination. The importance of lumbar puncture has already been mentioned. If a fine needle is used (No. 20 bore) and the jugular veins are not compressed, there is probably little danger in doing a "spinal tap" in most cases. Nevertheless, the procedure should not be routine; in every case a decision should be reached at the time of the first examination as to the necessity of the procedure and the most appropriate time. If cerebellar or temporal lobe herniation is threatening, the lumbar puncture may contribute to a fatal issue and should be deferred unless absolutely necessary. This has been observed to happen in brain hemorrhage, massive cerebral infarction, cerebellar infarction, and hypertensive encephalopathy. In primary subarachnoid hemorrhage the lumbar puncture, although necessary for diagnosis, should not be repeated except to investigate the possibility of further hemorrhage. It is not advisable to attempt to remove the blood in the cerebrospinal fluid by repeated punctures.

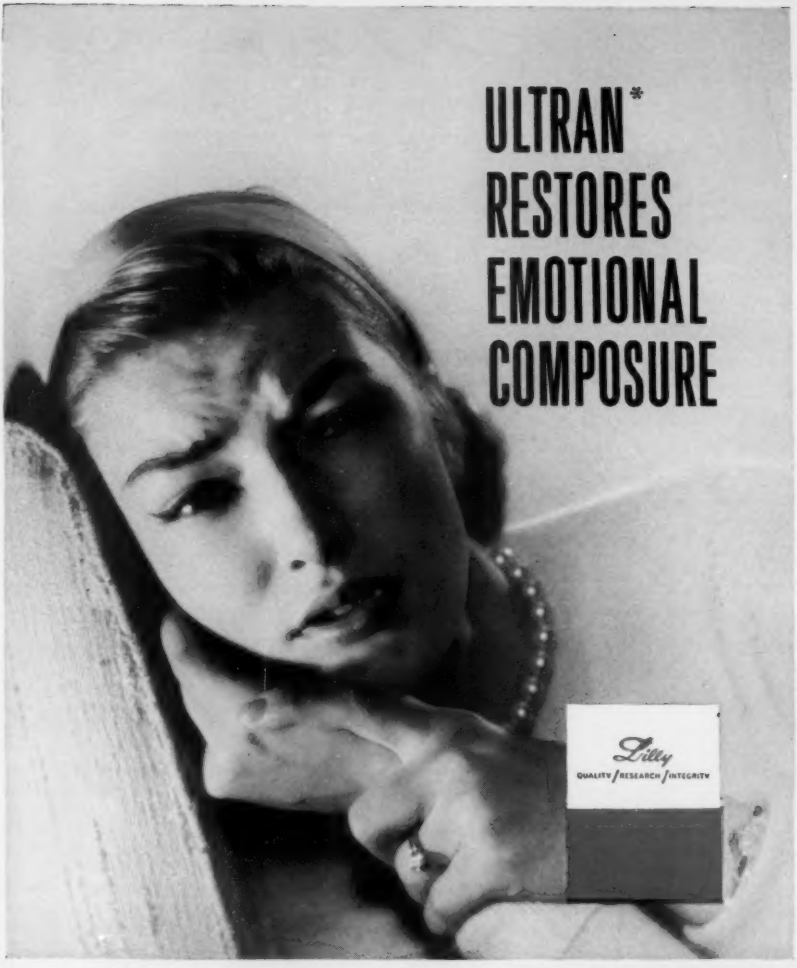
Many patients with apoplexy should have roentgenograms of skull en route to the ward, especially if there is any suspicion of trauma. The finding of unexpected fractures, a displaced pineal gland, or calcification in an aneurysm or vascular malformation will be helpful in diagnosis. A chest roentgenogram is useful as part of the cardiac examination and sometimes will disclose a dissecting aortic aneurysm or a pulmonary tumor.

Blood cell counts also provide useful information. A high hematocrit suggests that polycythemia is a factor; a severe anemia and greatly increased sedimentation rate might provide a clue to the existence of subacute bacterial endocarditis and should lead to a blood culture. Leukemia and thrombopenia, of course, must be diagnosed from the blood examination. A polymorphonuclear leukocytosis, not infrequent in cerebrovascular diseases, is most marked in hemorrhage where levels are often above 20,000 per cu. mm., and in infarction where the range is more likely to be 10,000 to 20,000 per cu. mm. Leukocytosis is also a frequent finding in aneurysmal rupture with subarachnoid hemorrhage. In the latter condition there may also be a transient albuminuria and hyperglycemia with glycosuria. Hypertensive hemorrhage, too, can cause hyperglycemia. Blood serology and a spinal fluid Wassermann test should be done.

An electrocardiogram should be obtained in all cases of cerebral infarction. Occasionally it will establish the presence of a recent, silent myocardial infarct. An electroencephalogram is *abnormal* in most major strokes and is a useful means of following the natural course of the illness. However, its utility in cerebrovascular diagnosis has yet to be determined.

Carotid arteriography is indispensable in the diagnosis of aneurysms and vascular malformations. Some 75 to 80 per cent of such lesions within the territory of the carotid arteries are revealed by this method. It always carries some risk and we have not, therefore, favored its use in cerebral infarction, except in a few cases of suspected occlusion of the internal carotid artery. In these cases retinal arterial pressure measurements have also been of help.

By the assiduous application of clinical method and laboratory test, a diagnosis of the type of cerebrovascular disease can be made with approximately 75 per cent or higher accuracy.



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The Lederle Laboratories Division of the American Cyanamid Company announced that it is making available to medical schools throughout the United States and Canada "Lederle Medical Student Research Fellowships" for the year 1958.

These fellowships, in amounts not exceeding $600.00 per year for any one individual, are intended to relieve in part the financial burden of students who desire to devote their summer vacations to research in the preclinical departments. Students who apply for these fellowships must be of good scholastic standing and must have the consent of the faculty member under whose supervision their research is to be conducted. The selection of students to receive such awards will be made by the dean of the medical school.

WALLACE LABORATORIES INTRODUCES 'MEPROSPAN', PROLONGED RELEASE FORM OF MEPROBAMATE

"Meprospan," a new, prolonged release capsule form of meprobamate that permits evenly sustained relaxation of mind and skeletal muscle — often at half the dosage required by meprobamate tablets — has been introduced by Wallace Laboratories, New Brunswick, N. J. Each capsule contains 200 mg. of meprobamate in the form of coated pellets which release the drug continuously for 10 to 12 hours. Advantages cited for the new form include sustained effect and dosage reduction, a simplified dosage schedule and a reduced possibility of side effects. Indications are the same as those for the standard tablet form of meprobamate: anxiety and tension states and related conditions, such as insomnia, premenstrual tension and tension headache; and skeletal muscle spasm in rheumatic conditions and in certain forms of cerebral palsy. "Meprospan" is packaged in bottles of 30 yellow-and-white capsules.

WARNER-LAMBERT ANNOUNCES FORMATION OF RESEARCH INSTITUTE

The establishment of a Warner-Lambert Research Institute has been announced by Warner-Lambert Pharmaceutical company. Heading the institute will be Dr. Earle Arnow, who will assume responsibity for the over-all administration of research of the various divisions of the company. The establishment of the Warner-Lambert Research institute is an important step in the program to consolidate and strengthen all of the company's major research activities. Headquarters of the new institute will be at the company's headquarters in Morris Plains, where a new research laboratory building for its Warner-Chilcott Laboratories division was dedicated just a year ago.

Before entering the pharmaceutical industry, Dr. Arnow was on the faculty of the University of Minnesota. He holds the following degrees: B.S. and Ph.G., University of Florida; Ph.D., M.B. and M.D., University of Minnesota. In addition to publishing a large number of scientific articles and reports, Dr. Arnow is the author of several textbooks on chemistry, pathology, and biology. In 1953, Dr. Arnow was the recipient of a Centennial Award from the University of Florida, and in 1955 he received an Outstanding Achievement Award from the University of Minnesota.

(Continued on page 19A)

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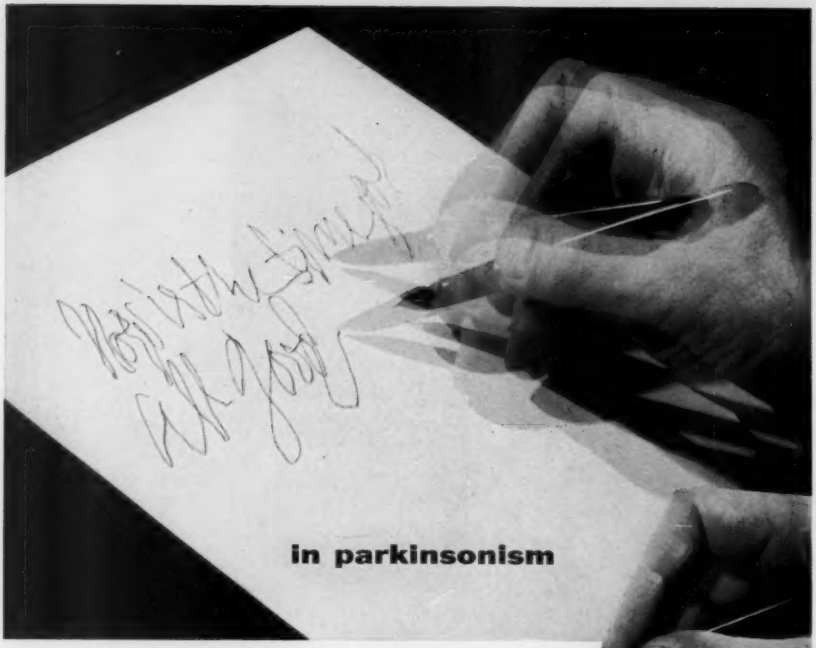

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Most patients can be controlled with a maintenance dosage of 50 mg. four times daily. However, more severe cases may require up to 600 mg. daily, a dosage level ordinarily well tolerated.

References: 1. Doshay, L. J.; Constable, K. and Agate, F. J., Jr.: J.A.M.A. *160*:348 (Feb.) 1956. 2. Berris, H.: J.-Lancet *74*:245 (July) 1954. 3. Timberlake, W. H. and Schwab, R. S.: N. Eng. J. Med. *247*:98 (July 17) 1952.

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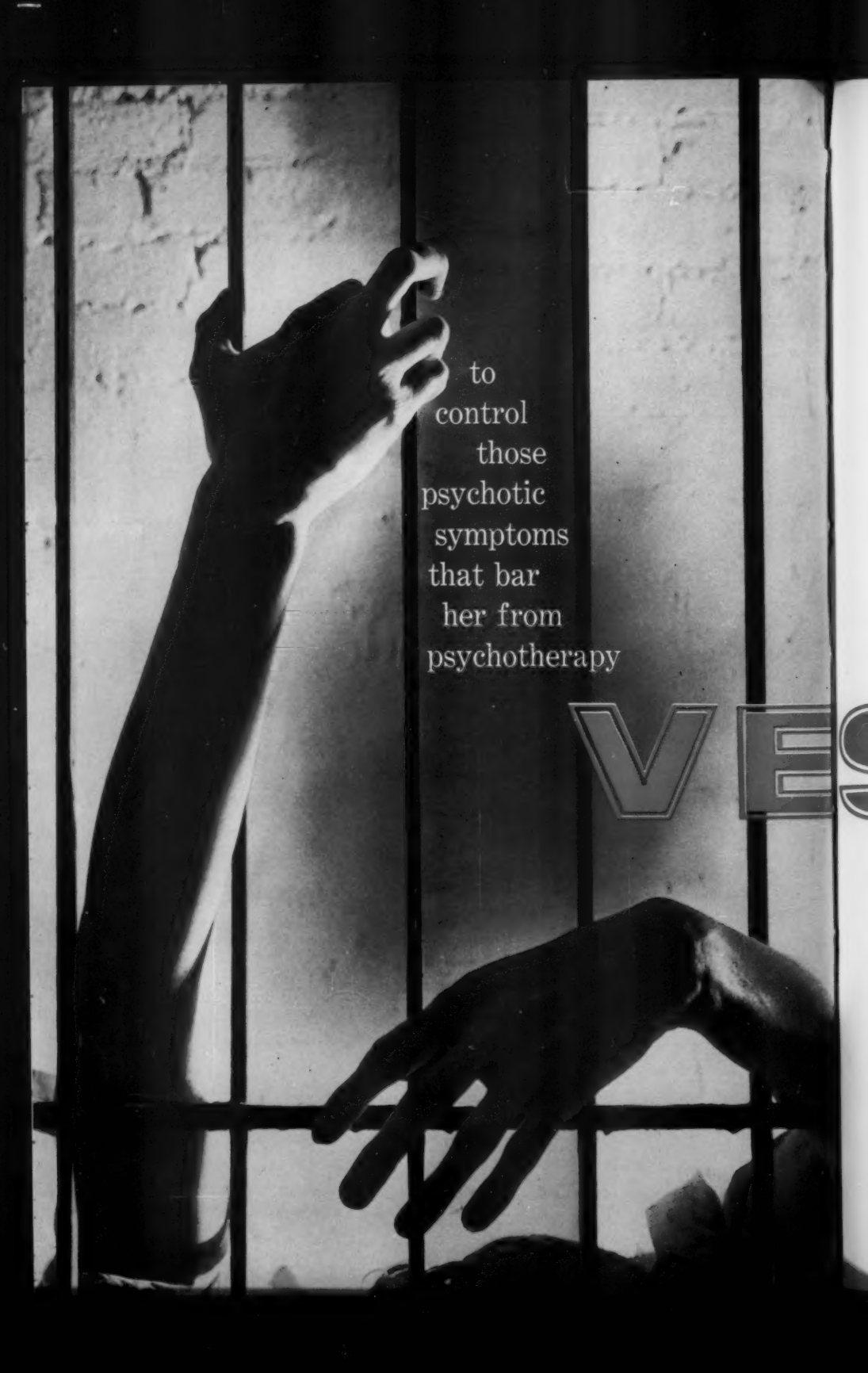
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(Continued from page 14A)

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AET is supplied through the Chemical Sales Division of Abbott Laboratories.

SQUIBB INTRODUCES VESPRIN

Vesprin, a new phenothiazine derivative, especially valuable for the treatment of psychotic patients, is available from E. R. Squibb & Sons, New York City. Useful in schizophrenic, manic states and other psychoses such as organic brain disease, Vesprin is also effective as an anti-emetic and anti-nauseant as well as for the alcohol withdrawal syndrome. Extensive clinical trials have shown Vesprin to be effective in controlling active psychotic manifestations. The new Squibb drug ameliorates such psychotic symptoms as delusions and hallucinations. It was found to modify intractable psychotic behavior patterns, controlling agitation and panic, as well as agrressive and hostile behavior.

Clinicians who have worked with the drug over long periods report it to be singularly free from toxicity. No cases of jaundice or liver damage, or convulsions have been reported in patients treated with the drug. Photosensitivity has been observed infrequently and hyperthermia rarely. Vesprin is supplied in oral tablets of 10 mg., 25 mg., and 50 mg., in bottles of 50 and 500 and in parenteral solution.

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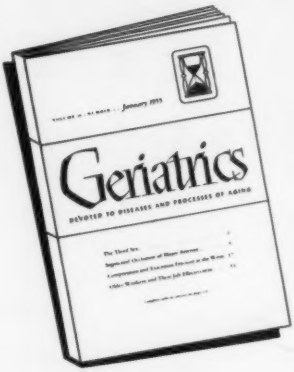

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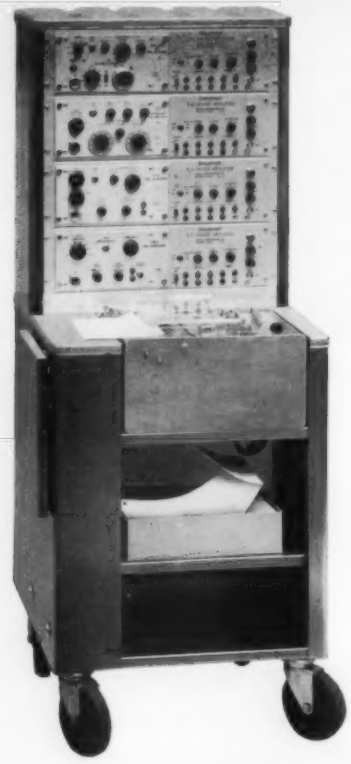

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MAY 1958

New AAN Members Since 1958 Directory Eighty-six physicians and scientists have been added to the membership roster of the American Academy of Neurology since the recent publication of the 1958 edition of the AAN directory. On the new list, which includes five active members, 44 associate members, and 37 junior members, are: Artur Abramowicz, James A. Bain, Claude Belanger, Ewart G. Bertram, David I. Biser, John H. Bornhofen, Sarkis L. Broussalian, John A. Broward, William Brown, Nathaniel A. Buchwald, John R. Calverley, Bland W. Cannon, Raul Carrea (Buenos Aires), Louis W. Conway, John B. Decker, Sevim Eker, Lawrence A. Farber, Alexandra Feldmahn, Robert G. Fisher, Marie Fleming, George C. Flora, Robert Flynn, Joseph H. French, W. A. Froelich, Jose L. Garcia-Oller, Murray Glusman, Rahman Goodarzy (Tehran), Walter J. Grant, Arnold H. Greenhouse, C. G. Gunn, James N. Hayward, Wayne Herbertson, R. A. Hughes, John G. Humphrey, Kenneth Kapphan, W. E. Karnes, Herbert R. Karp, Sidney Keats, Robert F. Kibler, Rodger S. Kirkegaard, Hallgrim Klove, Melvin M. Kramer, Jordan H. Lachman, Lionel H. Lemieux, Simeon Locke, John J. Lowrey, Sara A. Luse, J. Neil Marshall, Violet B. Matovich, Guy M. McKhann, William M. McInnis, John H. Menkes, Brewster S. Miller, James A. Moriarty, DeLora F. Mott, William E. Murray, Arnold Nevis, William T. Newsom, Edward Norton, Harold D. Paxton, Gustavo F. Poch (Buenos Aires), Fernand Poirier, James H. Pollex, Robert W. Porter, Jerome B. Posner, John N. Potanos, David A. Prince, Abdul N. Rahman, Francis W. Ramsey, Richard K. Richards, Zack W. Sanders, E. Carl Sensenig, Melvin Simonson, Alfredo E. Socorras, John O. Strom, Samuel S. Sverdlik, Chester A. Swinyard, Robert Terry, Juergen E. Thomas, W. W. Thompson, Stephen Vogel, I. David Waitzel, John R. Wherrett, William Wolfe, Allan W. Wright, Ronald Youmans.... The total AAN membership now stands at 1,840, of which nine are honorary, 51 honorary corresponding, 749 fellows and actives, 713 associates, and 318 junior members.... Inquiries on AAN membership should be sent to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

AAN Becomes Cooperating Society in NAS-NRC The American Academy of Neurology has been appointed as a cooperating society in the Division of Medical Sciences of the National Academy of Sciences-National Research Council, Washington, D. C. Since the American Neurological Association already was a

cooperating society in the NAS-NRC, it was decided that the ANA and AAN be represented by a single nominee, which is the usual practice when there are two cooperating societies representing a single field. Accordingly, President Francis M. Forster has been appointed as representative to the NAS-NRC, for both the ANA and the AAN, for the three-year term beginning this May.

American Board Plans Foreign Certification The American Board of Psychiatry and Neurology intends to provide a program for special foreign certification of physicians who are not residents of the United States or Canada, who do not hold a license to practice medicine and who do not contemplate engaging in medical practice in these countries. The plan calls for these special foreign certifications by a certified examination after the completion of certain prescribed requirements.... For further information, communications should be forwarded to Dr. David A. Boyd, Jr., Secretary-Treasurer, American Board of Psychiatry and Neurology, 102-110 Second Ave., S. W., Rochester, Minnesota.... The next board examinations will be held in New York (Dec. 15-16, 1958) and in New Orleans (March 16-17, 1959).

Training Fellowships in Neuroanatomy and Neurophysiology Beginning in September 1958, the New York University - Bellevue Medical Center offers a three-month training fellowship program with individual stipends in neuroanatomy and neurophysiology. For further information, inquiries should be addressed to Dr. Louis Hausman, Department of Anatomy, New York University-Bellevue Medical Center, 550 First Avenue, New York 16, N. Y.

Pennsylvania to Continue Research Fellowship Program The Institute of Neurological Sciences, School of Medicine, University of Pennsylvania, announces a continuation of its training and research fellowship program which is geared to a broad and integrated study of the nervous system. The institute also has fellowships available to support qualified investigators who wish to pursue an academic career in psychiatry. These fellowships are available to Ph.D. candidates and to postgraduate investigators (Ph.D., M.D.). Stipends vary according to individual needs and qualifications.... Further information may be obtained from Dr. Louis B. Flexner, Institute of Neurological Sciences, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

Basal Ganglia Surgery to be Subject of New York Symposium The New York University-Bellevue Medical Center and St. Barnabas Hospital are to stage a three-day symposium on Basal Ganglia Surgery for Involuntary Movement Disorders in the Alumni Hall Auditorium of New York University-Bellevue Medical Center, 550 First Avenue, New York 16, New York (May 15-17, 1958). The meeting is sponsored by the American Rehabilitation

Foundation and the Sister Elizabeth Kenny Foundation. On Thursday, May 15, the scientific session of the symposium, of which Irving S. Cooper is general chairman, will open with discussions on Neuroanatomical and Physiological Considerations Related to Basal Ganglia Surgery in Humans, to be moderated by Ray S. Snider. Next, the Technical Aspects of Surgery of the Basal Ganglia in Humans will be discussed, with A. Earl Walker moderating. On Friday, May 16, the Results and Effects of This Type of Surgery in Humans will be presented by Irving S. Cooper and Robert S. Schwab, with Percival Bailey moderating. The other panel members are Derek Denny-Brown, A. Earl Walker, and S. Bernard Wortis. On Saturday, May 17, Irving S. Cooper will moderate a panel discussion on the Neurologic and Physiologic Implications of Current Investigations of Basal Ganglia Operations in Humans. Included in this panel is Howard A. Rusk, professor of physical medicine and rehabilitation, NYU College of Medicine.... Inquiries about this symposium should be addressed to Miss Dorothy P. Frome, Office of Public Relations, 550 First Avenue, New York 16, New York.

Cerebral Palsy Group to Meet in Providence

The annual meeting of the American Academy for Cerebral Palsy will be held at the Sheraton-Biltmore Hotel, Providence, Rhode Island (Sept. 25-27, 1958). The program will comprise instructional courses, a special symposium arranged by the research committee, of which Chester A. Swinyard is chairman, and sessions devoted to the presentation of scientific papers. The chairman of the program committee is Dr. William Berenberg, The Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts.

The Alumni Meeting of Washington University

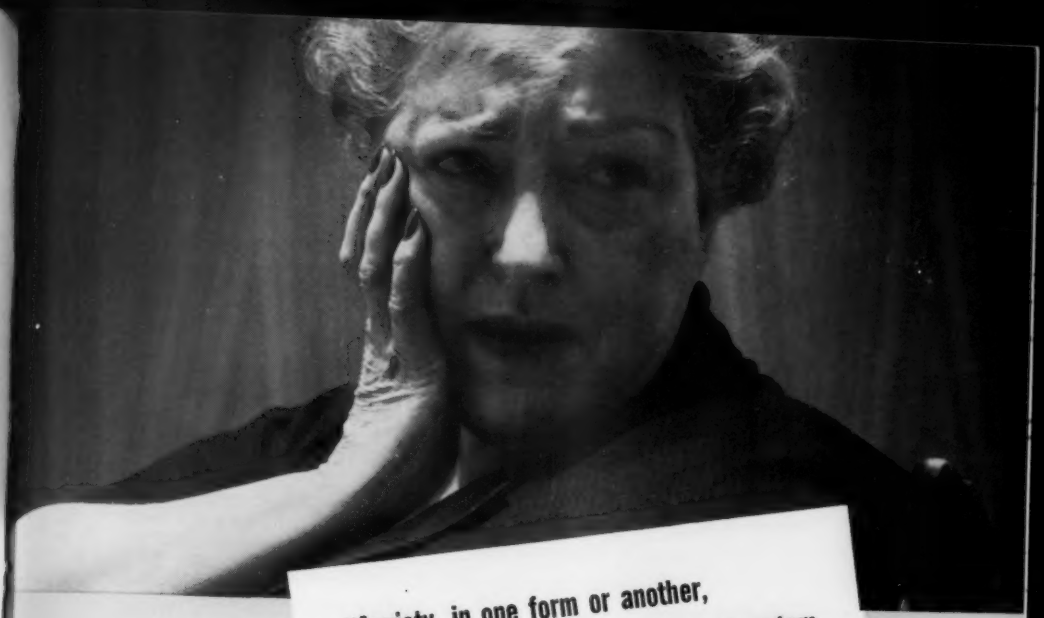
Annually the Washington University neurology-neurosurgery alumni convene in St. Louis for a well attended neurologic conference. This year it took place on April 11. At the morning session, chaired by Hallowell Davis, the Washington University alumni gave their presentations. Following welcoming remarks by Dean Oliver Lowry and an introductory address by Henry G. Schwartz, cerebellar functions were discussed by R. S. Snider and K. Sato; trigeminal potentials by R. B. King; after-positivity in geniculate neurons by Edward Vastola; the significance of fiber size in the central action of anesthetic agents by W. F. Collins and C. T. Randt; stimulation of the cerebellar and motor cortex by F. Morin and H. D. Portnoy; intracranial aneurysms by W. E. Hunt and J. N. Meagher; and electrical activity in a simple (?) brain by Fernando Orrego.... For the afternoon session, there was an invitational symposium entitled "Membrane States: Excitation and Inhibition," moderated by James L. O'Leary. Among the participants were Theodore Bullock, Alexander Forbes, Harry Grundfest, Herbert Jasper, Stephen Kuffler, Wade Marshall and Ichiji Tasaki.... The subject of the annual George H. Bishop Lecture in Experimental Neurology was "Generation of Nerve Impulses in Receptor Organs,"

given by Michael G. F. Fuortes of the National Institute of Neurological Diseases and Blindness.

Forster Resigns as Dean of G. U. Medical School AAN President Francis M. Forster has resigned as dean of Georgetown University School of Medicine. However, he will retain his post as professor and director of the Georgetown department of neurology. For some time he has wished to devote full time to his neurology program.... Dr. Forster's successor is Hugh H. Hussey, director of the school's department of medicine, editor of GP, the journal of the American Academy of General Practice, and a trustee of the American Medical Association.... Dr. Forster was called to the White House recently as a consultant to President Eisenhower; also, he was just nominated to the Advisory Council of the National Institute of Neurological Diseases and Blindness.

New Classification of Cerebrovascular Disease In the May issue of NEUROLOGY, there is a special section, entitled "Classification and Outline of the Cerebrovascular Diseases" by Clark H. Millikan and his committee of collaborators. The purpose of the study, which has been underway since September 1955, is to provide a preliminary tool for cooperative multidisciplinary and multi-institutional research in this field. The article sets forth criteria for the definition, classification, and general clinicopathologic aspects of cerebrovascular disease in the light of our present knowledge.... Reprints may be obtained without cost from the National Institute of Neurological Diseases and Blindness as long as the supply lasts.

Percival Bailey



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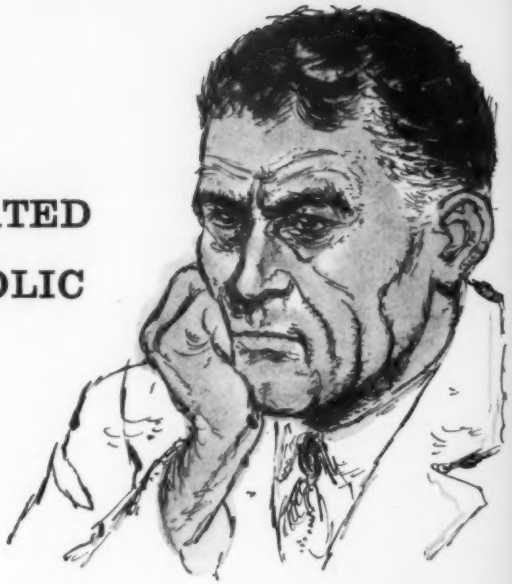

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